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FAMILY STUDIES IN PREVENTIVE PEDIATRICS*

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WHEN John Clarence Cutter founded this lectureship and decreed that the lecture must be delivered in Boston and free to the medical profession, to the public and to the press, he was probably prompted by the zeal for education that had taken him many years before to his teaching post in Japan. But as I look back I believe that he was influenced also by Lemuel Shattuck's *Census of Boston*, a book so famous that a British historian has recently described it as "one of the most remarkable documents in the annals of public health, which might serve as an ideal even today." While I handled that book in your library this afternoon, as a runner might make a trial sprint before his race, I could only hope that, in attempting to describe some field studies in medicine and their application to clinical education, I might catch a little of the spirit of that book and these two men.

In this Cutter Lecture, with its honorable history of discovery so well expounded year by year since 1912, I need say little of the history of preventive medicine. Nor need I dwell for long on the great achievements of pediatrics within that field of human endeavor. We have traveled far from the eighteenth century, when Gibbon, himself the sole survivor of seven children, could write of the death of an infant as "an unfortunate but highly probable event"; far also from last century, when a third of the children died before they reached the age of ten; and even from the beginning of this century, when nearly a fifth of the children born in our towns died within a year. The story from that point is a record of advance and victory until now the death of a child is regarded as a calamitous event that must be inquired into. The major pestilences are under control. Our infantile mortality in good environments is nearing an irreducible minimum. If there is still a pitiable waste of life in the neonatal period, the health of older children is remarkably secure. Taking neonatal deaths at a level of 20 per 1000 as a basis, there are pro rata more deaths in the first month of life than in the whole next twenty years of life. In England, with its 42,000,000 population in 1945, only 899 children died at the age of five, and 438 at the age of eleven. There is only a 1.19 in 1000 chance of a child's dying in any single year between the age of five and ten, and less than a 1 in 1000 chance in any year between ten and fifteen. In the twelfth year of life, when death rates are lowest, the chance of dying is 1 in 1280. This may be too optimistic a picture, and I do not wish to suggest that there is not more yet to be done. We are left with preventable deaths and disablement in childhood that come from trauma, from genetic faults, from tuberculosis and from the uncontrollable infectious diseases that remain with us. We are faced also with the dangers that will arise in our attempts to adjust ourselves to our new technologic and comfort-providing environments, as is seen, for example, in the new epidemic constitution of poliomyelitis.

Against this achievement of preventive pediatrics in controlling disease and fostering health, we must set the diminishing birth rate. In any final act of biologic accountancy this must be taken into consideration, particularly in judging the effect of the diminishing birth rate on the size of the family and the subsequent effect of the small family on the virtue, character and mental health of parents and children.

Many hands have gone to make this progress in preventive pediatrics. But as a clearer understanding of a problem is best approached by a clear analysis of the facts, I should pick out first for praise the inquirers who have used statistics to reveal the facts. The story of these begin with Graunt, who first published his "Natural and Political Observations on the Bills of Mortality" in 1662. He had to work with crude machinery, which he describes as follows in his sixth edition of 1676:

> We have hitherto described the several steps whereby the Bills of Mortality are come to their present state. We come next to show how they are made and composed, which is in this manner, viz: When anyone dies, then either by tolling or ringing a bell, or by speaking, for a grave of the sexton, the same is known to the searchers corresponding with the same sexton. The Searchers hereupon (who are antient matrons sworn to their office) repair to the place where the dead corps lie and by view of the same and by other enquiries, they examine by which disease the corps died. Hereupon they make their report to the parish clerk, and he every Tuesday night carries in an account of all the burials and christenings that week to the clerk of the hall. On Wednesday the general account is made up and printed, and on a Thursday published and dispersed to those several persons who will pay four shillings per annum for this.

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Graunt's methods were crude, but a start had to be made somewhere, and he was a modest man and excused himself by saying "there is much pleasure in deducing so many abstruse and unexpected inferences out of these poor despised Bills of Mortality." We follow the growth of these methods by the Prussian Chaplain Johann Peter Sussmilch, William Farr, Simon, Creighton, Shattuck, Chapin, Greenwood and many others, to whose energy of mind and heart we must pay tribute.

In another field the facts were revealed by the early clinical pediatricians who were delineating for us the nature of disease in childhood, and this is the second group I choose for praise. Here I need go back only a short distance in time, because clinical pediatrics as we know it, had to break away from general medicine to devote itself to its intensive studies. Established as it was near the end of the nineteenth century, it was shaped by two prevailing influences, the dominance of the hospital as the place for clinical research and the rise of laboratory medicine. Its scope was limited by these influences, but nevertheless it had and continues to have great successes, because diseases cannot be prevented until first they are understood. To mention the names of Koplik, Barlow, John Thompson, Holt, Blackader, Czerny, Finkelstein, Feer, Pirquet, Howland, Park and Jundell reminds us how much understanding of pediatric diseases has been revealed in the past fifty years by the elucidation of clinical facts, and by the explanation of many of these facts in laboratory researches.

Medical statistics, hospital pediatrics and laboratory research work are not entirely sufficient in themselves, and yet another group of workers deserves notice. These are the field workers who have gone outside the hospitals into the community to study the incidence and spread of disease, the effects of social conditions on disease and the control of disease and promotion of health by social environment. Some of this work has been done by sociologists, but mainly by medical practitioners, and it is fashionable to speak of their methods as "social medicine" or "environmental medicine." I must confess that I dislike these arbitrary definitions, which suggest that this field work is something entirely distinct and apart from clinical and laboratory medicine. I would rather take the view that a considerable number of the team who work in social or environmental medicine must be clinicians and laboratory workers who go out to work in that field whenever their problems take them there. By such methods rickets has been overcome. Such work, as described by Ryle, goes further than the scope of "public health" as we have known it in the past. Deriving its inspiration from clinical experience, it places the emphasis on man and endeavors to study him in relation to his environment. These field workers are the modern equivalent of Graunt's "Searchers." It is of these researchers and their methods that I propose to speak.

The methods of field inquiry in clinical or environmental medicine vary with the purpose of the study and with the training and experience of the workers. In this respect it is no different from other methods of research. The chief difference is that field inquiries are laborious, diffuse and difficult to control with scientific standards. It may help us if I attempt to portray some of these difficulties and state some underlying principles of method.

The research must be designed to a definite and worthwhile end. Too many field inquiries are worthless because they are trivial, as the counting of pebbles on a beach would be trivial.

When these studies are undertaken in homes and families they must observe a strict ethical standard that does not invade the rights of privacy.

The sample chosen for study must be adequate in size, and the duration of the inquiry adequate in time.

The investigators must be familiar with the structures of the sample by their own direct experience, in the same way as clinical researches must have a prior knowledge of human anatomy, physiology and pathology. If the sample has a local culture or local peculiarities the inquirers should know the locality and speak the dialect.

The method of collecting facts must be predetermined, and its accuracy and relevance must be tested.

The members of the team (if the investigation demands more than one researcher) must be familiar with, and as far as possible, expert in each other's technics.

With these precautions in mind, it is evident that some inquiries in social medicine can best be carried out by a medical practitioner who lives in his community as the "family doctor" and uses his families as his material to be studied and recorded year by year and from one generation to another. This was the method of Jenner as it is the method of my neighbor Dr. Pickles, a predecessor of mine in these lectures. But not many men in general practice have the time or training or inclination for such work. In pediatrics we shall need this method if we are to study the genetic constitution of disease, and the epidemiology of some of the indefinable infectious diseases of infancy. It will be a necessary method also when we come to study the technics of family life, the capacity of parents to play their part in preventive pediatrics. This thought must have been in the mind of a writer of a plaintive letter in the *British Medical Journal*, who said, "An intelligent community that really wished to improve its health would put its best doctors into general practice

and give them sufficient leisure to research into the problems of real life."

But the isolated inquiries of a medical practitioner are applicable only to limited subjects. More extensive research may be necessary for other particular purposes, and for these a more complex organization will be required. This brings me to speak of a personal experience of field inquiries in clinical preventive medicine designed to be a component part of the work of a university department of pediatrics with a comment on its effect on teaching and practice of pediatrics.

The Medical School and Teaching Hospital of my university is in an industrial city of 300,000 people with a contiguous and neighboring population of over 1,000,000. The Paediatric Department carries a heavy responsibility of routine clinical work in wards, in outpatient consultation services and in laboratories. That part of its work is impelled by the usual interest that now prevails throughout the world in diagnostic and therapeutic medicine. A new physical sign is eagerly seized. A rare disease is exciting news. A miraculous case is the very breath of life to all of us, particularly to the young men who find complete intellectual interest in that type of medicine at that stage of their career.

Wishing to widen our experience beyond the wards and laboratories, we have set aside a team of field workers who work largely as the research department for the city health authority in social and preventive medicine. It is a two-way process. We present problems to the city authorities, and they bring their problems to us. We did some early surveys in differential growth and development of children in various social groups, but our interest was not firmly established until the city asked our advice on its rising infantile mortality between the years 1935 and 1938. The health authorities were disposed to counter this by opening more child welfare clinics. But after consultation it was agreed that it would be better to get the real facts on death and disease in the city, before making expensive programs, which may savor of Chapin's advice "when the facts are not at hand have the courage to do nothing." We undertook to organize a detailed and personal investigation, first on a sample of infant deaths in the city, with their relevant familial, economic, social and clinical features, and later a similar inquiry into morbidity, particularly of the acute infective illnesses as they arise in the homes of the people. The research had the designed purpose of providing facts in which we could advise the city health department about its child welfare program. The mortality study continued throughout 1939. It was carried out personally by Dr. F. J. W. Miller, with occasional help from me and the part-time services of one clerk. In that year there were 272 infant deaths in the city. We were able to make an immediate and adequate inquiry into all but one of these. Our results were not remarkable, but they gave us hard facts with which to argue, and we were able to reveal the wide disparity between the notified cause of death and the true cause of death, thereby pointing the way to a need for better vital statistics on infantile mortality.

The benefit of this study was mainly to ourselves in giving us experience of method that involved the quick and spontaneous co-operation of all the doctors, hospitals, nursing homes, and health officials in the city. We acquired a technic. Out of this has grown a companionship that now serves us well. The war interrupted us, and we were not able to resume the second part of it until later.

In 1946 we began to design an investigation of infant morbidity for the city. Its main purpose was to study by direct observation the acute infective illnesses of infants. We wanted to know the incidences, the clinical types and the results of these diseases studied against the background of the homes and families in which the patients lived.

We had in mind three other long-term purposes. The first was to widen the interests of the young men working in the wards and laboratories, by bringing them in daily contact with the field searchers. The second was to provide ourselves with relevant local facts wherewith to freshen our clinical teaching and to guide health programs. The third was to create a method to give us a contemporary picture of disease verified by statistics and direct clinical observation, which would reveal new problems for research.

We spent several months preparing our methods of inquiry. These included meetings with the medical practitioners of the city, whose co-operation was essential; a precise liaison with the public-health department, with whom we have kept in step at every stage until they regard it as a joint research; a co-operative arrangement with all hospitals and nursing homes; and a study of methods of entering into the homes in a manner that would make us welcome. In that preliminary period we busied ourselves with assembling a team of workers, and in determining the sample to be studied and the method of making observations and records.

We decided that a sample of about 1000 infants should be taken and studied from the day of their birth. This represented about a sixth of the city's births in a year. We had the alternatives of picking every sixth child or taking all the births in a sixth of the year. We chose the latter, and decided on all the infants born in the months of May and June, 1947. This gave us an easily identifiable sample. From then on we could recognize and easily remember that a May–June baby was in the sample — or a "red-spot baby" as they came to be known. The choice of May and June was deliberate, having the advantages of

allowing us to undertake the initial heavy work at a good season of the year.

The number of infants born in these two months was 1142, representing a complete cross section of all social groups of the city. Out of this total there were 6 nonco-operators, 2 of whom were doctors. This is some index of the success of our methods of approach. It is necessary here to indicate that the people of the North of England are mainly indigenous, shrewd and independent, suspicious of strangers and great home lovers. Their successful co-operation was, I think, mainly due to the courtesy of the preliminary explanation given to the parents by doctors whom they knew and trusted. They were promised no rewards or benefits. They understood clearly that we were there only to observe and understand their difficulties.

TABLE 1. *Social Classes by Occupation of Father.*

CLASS	NO. OF INFANTS
Professional	32
Blackcoated workers	93
Artisan	602
Semiskilled	172
Unskilled	163
Not classifiable (largely illegitimate)	80
Total	1,142

Samples chosen in this way will vary with the social structure of the city. The structure of our sample is illustrated by Table 1. The incidence of illegitimacy also has an influence on the sample. In ours it was 5.7 per cent (65 in 1142). The place of birth was a factor for consideration both for the purpose of comparison and for the etiologic studies of infection (Table 2).

TABLE 2. *Place of Birth of Infants in the Sample.*

PLACE OF BIRTH	NO. OF INFANTS
Home	655
Hospital	353
Nursing home (private)	131
Not determined	3

After this glimpse of the sample I return to method. We took 5 nurses who were health visitors and trained them in our methods. We knew the sort we wanted, and we got them. They sat in on the preparation of the inquiry. Each of them took about a fifth of the families as their parish. It was their duty to make themselves intimate and familiar with their parishioners or, to put it more pompously, to understand their social anatomy and physiology. The first visit to the home and family was the most important. The nurse then established a relation, and all else followed easily.

By previous experience we determined at what intervals a regular visit should be paid by the nurse, and by a preliminary pilot survey we tested our methods. The technic was that she should make regular visits, gather all the relevant information at each visit and come again or call when necessary. Apart from the basic information about housing, living, feeding and working arrangements, which she collected with as much tact as possible, it was her main duty to collect the details of all illnesses or ailments however slight and to bring the doctors in on consultation whenever necessary. The inquiry was in the first place a study of the incidence, nature and results of infective illnesses. After experiments we found that a mother's memory of the minor ailments of her children was not accurate beyond seven weeks. On this finding the regular visits were arranged at intervals of six or seven weeks. Also, it confirmed my view that the questionnaire method would not suit our purpose.

The team was completed with 2 clerks, 1 doctor devoting most of his time to the research, and 2 other more senior pediatricians called in for special observations and studies. Each week's collected material was discussed, digested and collated at a Saturday conference. We brought to this the medical officer of health, his housing experts and others concerned whenever necessary. The complete records revealed in detail how a thousand families live and have their being, how their children are born and bred, what their ailments are, and the relation of these to others in the family. By direct experience and observation we know what has happened to these children. It has given us material both for social history and for clinical medicine. It started as a study of 1000 infants. It has become a study of 1000 families.

By the end of the first year the sample was disposed as follows: 44 had died, 6 had refused to co-operate, 125 had removed from the city, and 967 remained in the inquiry. The 125 removals were more than we expected. They reveal a temporary social difficulty due to a shortage of houses, by which young married couples returning from the war started their married life in lodgings or parents' homes until they removed to houses of their own.

The inquiry has now completed its second year, and we have decided to continue it for six years to come, mainly for the purpose of studying the familial pattern of disease, particularly respiratory illnesses and their late results such as bronchiectasis. Its records will be a formidable document, but the statistics will be vital. Already, they give a clear indication of how people live, how they cope or fail to cope with various difficulties, how they make use of their family doctor and what their attitude is to hospitals and health services.

I do not intend to display the clinical and epidemiologic results; I shall choose only examples to demonstrate how these may be used to give

reality to clinical teaching. To experienced practitioners of medicine there is nothing new in what I have to say, but it helps those who practice only in hospitals to broaden their concepts of disease and gives them practical material for teaching.

Whooping Cough

The simple clinical facts about whooping cough are easy to understand, but a clear picture of the disease in all its variations is hard to come by and still harder to demonstrate. The sample survey method gets near to it as our experience shows. Before they had reached the age of twelve months, 100 of our 1142 infants had whooping cough. The source of infection was intrafamilial in 41.

Of the 100 affected infants, 12 had severe whooping cough of the clinically obvious type, and of these 3 died; 65 had whooping cough intermediate in severity and difficult to diagnose on clinical grounds alone. The remaining 23 infants had the disease with symptoms so mild, lacking whoop or paroxysm, that diagnosis was reached only on epidemiologic or bacteriologic evidence. In these the illness took the form of a respiratory catarrh, with insignificant cough.

In the second year of the survey we saw examples of whooping cough in infants who had had the disease in the first year. The presumption is either that they had failed to develop immunity from the first attack, or that one of the illnesses was pertussis and the other parapertussis.

This intrafamilial method of clinical investigation gave us a simultaneous view of the disease in other members of the family and showed that whereas most of the older children had their whooping cough in its classic form, the disease could have been diagnosed with certainty on clinical grounds alone in not more than a third of the young infants affected. A knowledge of its intrafamilial epidemiology and its subclinical variations had to be called into assistance.

Let us look at the use of these clinical and epidemiologic facts in teaching. In the first place they give a topical picture of the disease, which could be continued year by year to demonstrate and calculate the trends of events. Possessed of this contemporary and serial knowledge with statistical confirmation, we can take the second step of evaluating a particular treatment or preventive program such as vaccination. In this way the student begins to see a disease from many angles. He is no longer looking at it through the blinkers of diagnostic medicine.

Other Intrafamilial Infections

One of the main projects of our investigation was to study the different types of respiratory illnesses and their results. While doing this we gain insight into the etiology of a variety of diseases including streptococcal illnesses, staphylococcal illnesses and tuberculosis. Here I use etiology in its literal sense to include the personal and environmental circumstances leading to infection. Working in this way from within our sample is like watching a play from behind the scenes.

Here I can do no more than pick out a few illustrations for general comment. We found nearly 60 of our families in which there was a long history of repeated staphylococcal infections, carrying with it a burden of considerable discomfort and disablement. These families demonstrate how defective medical treatment may be if it is merely episodic, and if members of the family consult different doctors or attend different hospitals. Only a doctor with a personal sense of responsibility for the whole family and knowing each member of it is likely to string together all the episodes of ten years to demonstrate the unity of the varying illnesses and to take steps to eradicate them, as he might eradicate scabies under similar circumstances. Our findings raise questions both of the carrier state within the family and of familial variations in immunity that may be genetically determined — a branch of serology that has received little study.

The method of investigation illustrated well the variations of disease manifestation according to the patient's age. To illustrate, I quote an example of respiratory infection. In a tenement building we saw a community of 22 people in 7 families. Through this community a respiratory infection spread over a period of eight weeks. All the 3 babies in 3 different families were severely ill, 2 with clinical pneumonia, and the other with bronchitis and constitutional symptoms: of the 6 children between the ages of one and five all had a respiratory illness of milder degree; of the 13 remaining older children and adults only 2 were affected, and they with only a slight catarrhal cough. This, again, is a good teaching example in which epidemiology linked to clinical medicine widens our view of a pathologic process in all its variations, and brings out well the factor of age in etiology.

Since our sample is a random selection including all classes of the community it gives us a clear indication of the clinical and social effects of tuberculosis. Regular tuberculin testing is the basis of this observation, and in this way we are getting exact information about the tuberculization of the group, seeing each child at the time of its primary infection and afterward. In this field the investigation acts as a constantly recording apparatus, pointing out where the danger lies and how it is operating. Even in so well worn a subject as tuberculosis we are being beset by new problems, of which one of the most interesting is the group of children under observation in infective families who fail to become infected. They remain tuberculin negative in spite of the risk. This is raising the question of the secondary factor, which arises to

determine the passage of tubercle bacilli through the skin or mucous membranes.

Conclusions

I cannot enter into more clinical details, and I have restricted my observations to a few illustrations of how field studies combining clinical medicine and epidemiology may be used to give a perspective view of a disease with its clinical variations, its age variations, its epidemiologic vagaries and its social effects. If they make no new discoveries they tie up a good many loose ends, and out of this experience the investigators will be able to advise on child health programs in a clearly determined order of priority. It also uncovers diseases and illnesses difficult to identify or to classify, and thereby poses new problems of research. Finally, it is creating an instrument of clinical observation correlated with exact statistics that gives authenticity to clinical teaching. I am encouraged to believe that John Clarence Cutter would have approved.

I have done no more than suggest how clinical study may be carried outside the hospital and the clinics. My final question must be to ask, Is it worth while, or is it mere pebble counting? The answer to this is given by my colleagues, Dr. F. J. W. Miller, Dr. Donald Court, Dr. Hugh Jackson and Dr. Ruth Fawcett, who are responsible for the work, the secretaries and the health visitors who assisted them so skillfully. They have brought together a wealth of detailed information from which we learn a great deal of clinical medicine and a great deal also about life itself, and the experience has transformed our own outlook on clinical medicine and clinical methods.

Whereas we had previously been concerned too much with diagnostic medicine and with the experimental study of phenomena, this field work has developed and confirmed an idea that has been in my mind for many years. Too much attention paid to diagnostic medicine diverts attention from the detailed study of the sequence of clinical events that makes an illness. A scientific study of this sequence of events, minutely observed, carefully recorded and with each event placed in its right time relation, is the method of the natural scientist, and it becomes a powerful instrument in the training of the young clinical scientist. To know the hourly or daily changes in the progress of an illness is clinical science of a different and higher order than mere diagnosis. To be able to recognize the slight but significant changes of typhoid fever that will take place between the seventh and ninth days of the illness requires greater skill than to diagnose the disease. By training in such work we become alert to the recognition of new syndromes or new diseases, and we become aware of the trends of disease in their epidemic fluctuations and clinical variations. Combined with statistically based field studies we thereby get a wholesome view of clinical medicine.

In the social field the chief lesson I have learned in our studies of disease in families is how well the people cope with their domestic difficulties. Less than 7 per cent are feckless or happy-go-lucky people who need help if they are to maintain a decent level of care of their children in health or sickness. The remainder are stalwart people coping with life and remaining loyal to their responsibilities.

PSYCHIATRIC FACTORS IN ESSENTIAL HYPERTENSION

II. Follow-Up Study of 74 Cases*

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IN A previous paper the findings of a psychiatric evaluation of 100 patients with essential hypertension were presented.[1] These patients were seen because emotional factors seemed important in the illness, or for opinion concerning the advisability of sympathectomy. The series is therefore weighted in favor of those with significant nervous factors. All the patients were under fifty-five years of age; a few were under thirty, but most were between thirty and fifty years. All the patients had a thorough workup in the medical department, and all but a few were free of any significant evidence of cardiac, renal or cerebral damage. The results of this study are shown in Table 1.

TABLE 1. *Data in 100 Hypertensive Patients.*

DATUM	NO. OF PATIENTS
Positive family history	65
Hypertensive personality	69
Other personality types	31
Preceding traumatic emotional experiences	65
No neurosis	32
Neurosis present	68
Prior to discovery of hypertension	44
Aggravated after discovery of hypertension	30
After discovery of hypertension	24
Aggravated by discovery of hypertension	17

The present report is on a psychiatric follow-up study of 74 of these patients after one year or more. A medical examination was carried out at the same time. Some of the patients had had bilateral dorsolumbar sympathectomy and splanchnicectomy; some had been treated by brief, simple psychotherapy involving three or more interviews. The largest number had had no specific treatment in the interim. Of these, most had been advised that no specific treatment was necessary. They were reassured and given suggestions regarding mental and physical hygiene.

So many variable factors are involved in hypertension that a controlled study is difficult. The present study is obviously not controlled, the follow-up period short, and the number of cases small. The results reported are not intended to have any statistical significance whatsoever, but only to indicate roughly the findings.

It was considered that the blood-pressure level was improved if there was a drop of at least 20 points systolic or diastolic, or both. The blood-pressure level was considered worse if there was an increase of 20 points systolic or diastolic, or both. If there was any evidence of increase in cardiac, renal or cerebral involvement, the patient's condition was also considered worse regardless of the blood-pressure level.

The patients were considered improved symptomatically if there was a definite improvement in symptoms of anxiety, headache, dizziness or fatigue and a better adjustment with an increase in capacity for work and activity. Obviously, there were some patients who showed marked improvement and became essentially symptom free, and others whose improvement was definite, but who still had symptoms.

TABLE 2. *Blood-Pressure Levels and Symptoms of 74 Patients One Year after Treatment.*

TREATMENT	TOTAL NO. OF CASES	BLOOD PRESSURE AFTER TREATMENT			SYMPTOMS AFTER TREATMENT			NO. OF DEATHS
		IMPROVED	UNCHANGED	WORSE	IMPROVED	UNCHANGED	WORSE	
Sympathectomy	18	16	1	0	15	2	0	1
Psychotherapy	13	4	6	3	11	2	0	0
Reassurance	43	9	22	6	20	13	4	6
Totals	74	29	29	9	46	17	4	7

Table 2 shows the findings in 74 patients in terms of blood pressure and symptoms after one year or more. In Table 3 these findings are listed according to the grade of the disease.

No specific conclusions are drawn from the results presented, but several things can be pointed out. Most of the patients having sympathectomy showed improvement both in blood pressure and in symptoms. Many of the patients receiving no treatment but mental hygiene and reassurance showed symptomatic improvement, the blood-pressure level remaining about the same. None of the patients receiving some psychotherapy were worse symptomatically. The important observa-

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tions, however, are brought out in the study of individual cases.

The first consideration pertains to the patients who died. Of these, 1 died from cerebral hemorrhage after the first-stage sympathectomy. The remaining 6 patients had received no specific treatment. Three of these, who died of cardiac diseases, had been advised to have the operation but refused. One patient who died of cerebral hemorrhage had an enlarged heart and probably should have been advised to have the operation. The other 2 patients, who had only a Grade I hypertension, apparently died of coronary-artery disease. In all these cases there was severe emotional stress.

The observation that many of the patients treated by sympathectomy showed definite, and at times marked, improvement in nervous symptoms raises the question whether the effect was due to the operation directly. Other factors besides the direct physiologic effect of operation can affect nervous symptoms as illustrated by the following case.

CASE 1. A 34-year-old married woman came to the clinic in February, 1947, for evaluation of her hypertension, which had been discovered in August, 1946. Medical study showed a blood pressure of 190/120, which was labile, impaired renal function with urinary albumin and Grade II changes in the fundi.

Psychiatric evaluation disclosed that she had always been a tense person who worried about others as well as herself. She had formerly had a "bad temper," which she had learned to control, keeping her fears and resentments to herself and trying to adjust herself to any situation. Two years previously her father had died of heart disease. Then her husband's father had died, there were altercations with the husband's family, her husband became ill, they were evicted from their home, and the patient became sick with severe headaches, fatigue and nervous symptoms. It was in this setting that the blood pressure was discovered to be high.

Bilateral sympathectomy and splanchnicectomy were performed in June, 1947.

One year later the blood pressure was 170/100 with the patient recumbent and 120/80 with the patient standing. There was no evidence of renal involvement.

There was no significant complaint of tension, headache or fatigue and no disability. She felt more relaxed than she ever had and stated, "I don't seem to worry as much as I did." She thought that her attitude had changed and that she did not take things as seriously, which she attributed to the operation. After operation she had found that problems at home straightened themselves out without her when she was unable to undertake the responsibility. She had followed advice regarding mental hygiene, particularly regarding emotional release.

This case is representative of hypertension, discovered in circumstances of severe stress, in a patient who had a typical personality background. After operation not only was the blood pressure level reduced but also there was good symptomatic improvement and an apparent modification of her personality reactions. The question is whether the latter was due to the physiologic effects of the operation or the psychologic factors accompanying it.

It is thus apparent that emotional and environmental factors can play a part in symptomatic improvement in the absence of specific psychotherapy. The patient's anxiety over his condition and the height of the blood pressure are lessened if an operation is performed that he is assured will, and actually does, reduce the blood pressure. The association with doctors in the hospital and later may well result in an alteration of habits and attitudes whether or not such an influence was specifically intended. The enforced period of disability and relief from the previous routine may also lead to an alteration of habits and attitudes and readjustment on a different basis. Environmental circumstances in the patient's life may change, thus leading to a better adjustment.

Even though these factors do operate, however, it is still possible that a direct physiologic effect is mediated through a reduction in the sympathetic outflow and a reduction in the blood pressure.

Before presenting the case of a patient treated with psychotherapy, it is appropriate to describe the type of psychotherapy used. In the previous paper[1] it was reported that 69 of 100 patients had personalities characterized by conscientiousness, worrisomeness, ambitiousness and emotional sup-

TABLE 3. *Blood-Pressure Levels and Symptoms According to Grade of Hypertension of 74 Patients One Year after Treatment.*

TREATMENT	TOTAL NO. OF CASES	BLOOD PRESSURE AFTER TREATMENT			SYMPTOMS AFTER TREATMENT			NO. OF DEATHS
		IMPROVED	UNCHANGED	WORSE	IMPROVED	UNCHANGED	WORSE	
Sympathectomy								
Grade I	3	2	1	0	2	1	0	0
Grade II	11	10	0	0	9	1	0	1
Grade III	4	4	0	0	4	0	0	0
Psychotherapy								
Grade I	7	2	3	2	5	2	0	0
Grade II	6	2	3	1	6	0	0	0
Grade III	0	0	0	0	0	0	0	0
Reassurance								
Grade I	26	4	17	3	15	6	3	2
Grade II	13	4	5	2	4	6	1	2
Grade III	4	1	0	1	1	1	0	2
Totals	74	29	29	9	46	17	4	7

pression, particularly suppression of hostile feelings. It was found that 65 of 100 patients had had preceding traumatic emotional experiences or conflicts. Finally, it was considered that of these 100 patients, 76 had significant secondary anxiety over their condition.

Therefore, the patients were encouraged to express their fears over their condition, misconceptions were corrected, and repeated and detailed reassurance was given. Specific conflicts and problems were discussed, with the object of insight and readjustment. Finally, an attempt was made to influence the patient to modify his habits and attitudes to some extent, particularly along lines of more freedom of emotional expression, and the need for relaxation in the planning of his routine was emphasized. The approach can be described as that of reassurance, insight and re-education. This is a superficial approach, but more intensive treatment was considered neither practical nor desirable.

CASE 2. A 43-year-old woman was first seen in 1945, when the blood pressure was 165/105; the hypertension had been discovered 11 years previously during pregnancy. In August, 1947, she was again seen because of an increase in the severity of symptoms of anxiety, along with headaches, dizziness and palpitation. The blood pressure was 188/110, but medical studies showed no cardiac or renal involvement.

On psychiatric evaluation it was found that she had always been worrisome but ambitious. She was particularly desirous of "having nice things" and tended to avoid arguments at all costs in order to prevent dissension. She always tried to control her feelings, confided in no one and harbored a great deal of resentment, particularly toward her husband. She had always been rather unhappy in her marriage, but since 1944, about the time that her symptoms began, her husband had become increasingly abusive to her and had been drinking to excess. For 3 years she had had severe anxiety over her condition, with acute fear of having a stroke or of dying, which at times prevented her from going out alone. She usually felt better when away from home and working, having most of her symptoms at night when at home, which she could associate with the presence of her husband. She had been in a great deal of conflict over whether to leave her husband, being deterred from doing so by fear over her own health and uncertainty of her ability to care for her children.

She was strongly reassured about her physical condition and her blood pressure. Her environmental problems were discussed with her, and she was advised that her physical condition need not interfere with any plans she might have, and she was given advice regarding mental hygiene. The acute anxiety symptoms improved with reassurance, and particularly so when she decided to institute divorce proceedings.

When seen a year later in August, 1948, she was essentially symptom-free; the blood pressure was 150/95, and medical examination was negative. She was working regularly, and was much less concerned about herself, but had not made much change in her habits or attitudes. The divorce decree had been obtained the previous June. The Minnesota Multiphasic Personality Inventory showed a reduction of the scores in the hypochondriacal and depressive scales below the neurotic range compared with the record of a year previously.

This case is an example of marked symptomatic improvement and decrease in the blood pressure after relief of secondary anxiety and the satisfactory solution of a mental conflict.

The largest group in this series was composed of patients who received no specific treatment. They had come to the clinic for consultation and study and at the conclusion of medical studies were advised that no operation was necessary. They had one psychiatric interview and were given reassurance and suggestions regarding mental hygiene. A few were advised to have bilateral sympathectomy but refused. It was considered that a number of these patients might benefit from further psychotherapy, but they could not return to the clinic for practical reasons, and psychiatric management was advised in the vicinity of their homes, but not obtained.

The follow-up study of these patients showed widely varying outcomes in the interval, which is to be expected because of the many factors involved. There are, however, several things to be learned, which can be best illustrated by the following histories.

CASE 3. A 48-year-old physician was seen in October, 1947, for evaluation of his hypertension of 7 years' duration. At the time of admission the blood pressure was 184/124. Medical studies showed no organic involvement except a slightly positive exercise-tolerance test by electrocardiogram. The hypertension was classed as Grade II.

Psychiatric study revealed a personality characterized by chronic tension, worrisomeness, conscientiousness and emotional suppression, with poor mental and physical hygiene. He had had increasingly severe headaches, fatigue, anxiety attacks and gastrointestinal symptoms. He admitted severe anxiety over his wife, who was apparently severely neurotic and maladjusted, and whose behavior he had been unable to cope with.

When the patient was seen a year later the blood pressure was 180/126, and there was no evidence of any progression in the organic status. He had been reassured after the previous study and had made definite modifications in his habits and attitudes. His wife's condition was much improved after psychiatric treatment, and there was much less strain at home. He had been essentially symptom free until 2 months previously, when a friend had died suddenly of coronary occlusion. After this he had developed increased anxiety over his condition, some headaches and palpitation and began to measure his own blood pressure frequently. The symptoms were not severe and were decreasing.

This patient had the typical personality and habits frequently seen, but was able to make definite modifications of his habits and attitudes. This, together with a relief of emotional stress, seemed to have a bearing on symptomatic relief. Recurrence of symptoms was associated with anxiety over his condition.

CASE 4. A 43-year-old woman was seen for psychiatric evaluation in October, 1947. Hypertension had been discovered in 1944, and since then the blood pressure had ranged between 156/108 and 220/120, but had dropped to nearly normal levels in the hospital at rest. Thorough study failed to show any cardiac or renal involvement. The history indicated that for at least 13 years the patient had had various somatic manifestations of anxiety from time to time, a marked tendency to anxiety over her health and fixation on bodily functions. Several episodes in the history suggested hysterical reactions. Since the discovery of hypertension the anxiety had been more acute, with phobias of going out or staying home alone and fear of impending "shock" or death, which had prevented any outside activities for 3 years. There had been a difficult problem in marital and sexual adjustments for many years. The overwhelming fixation on symptoms and health, together with the limited intelligence, prevented any evaluation of the underlying personality.

As the disease did not seem to be progressing and she was a poor psychic risk for operation, no drastic treatment was advised, and she did not return for further checkup until November, 1948. There had been no change for the better in her marital situation, and anxiety symptoms had been worse after her daughter was married. During the interval she had had several episodes of pain in the left side of the chest and left arm. In July she had lost almost complete vision in the right eye, which had since improved. The Minnesota Multiphasic Personality Inventory showed an increase in the scores on the hypochondriacal and hysterical scales in the neurotic range compared with the record of a year previously.

On examination the blood pressure was 190/120; it was labile, and the fundi demonstrated Grade III changes, with a massive hemorrhage in the right retina. Electrocardiograms showed left ventricular strain. Renal function was normal. Bilateral sympathectomy and splanchnicectomy were done in November, and she was discharged improved with a blood pressure of 140/82 in the supine position.

This case is an example of hypertension occurring in a severely neurotic patient, with aggravation of the neurotic symptoms after the discovery of hypertension, which progressed rapidly from Grade I to Grade III within a year, and the question arises whether the emotional stress and the neurotic reaction played a major part in aggravating the condition.

Case 5. A 48-year-old man was first seen at the clinic for evaluation of his hypertensive condition in February, 1947. Ten years previously he had been told that his blood pressure was high but had not been concerned about it until September, 1946, when he had visited his physician because of an acute attack of nausea, vomiting and diarrhea. He was told that his blood pressure was high and his heart enlarged and that he had angina because of palpitation and substernal tightness with emotional stress. He was advised to avoid all physical exercise and told that he must rest to avoid damaging his heart. An increase in tension, tremulousness and fatigue developed, with mild anxiety attacks. He became increasingly heart and blood-pressure conscious and in December stopped work in order to rest.

The blood pressure was 160/110; it was labile, and there was no cardiac enlargement or evidence of coronary-artery or renal involvement. The patient had always been worrisome and conscientious, critical of others who did not have the same standards, but insecure and sensitive to criticism. He was overly concerned about his blood pressure, and believed it would be dangerous for him to work.

It was decided that he was tolerating his blood pressure well and required no specific medical treatment. He was given strong reassurance and encouragement to return to work, along with suggestions regarding mental hygiene.

When seen 17 months later he had no symptoms but he had not worked for 1½ years. He made frequent visits to his physician to have his blood pressure checked. It usually ranged around 165/112. His physician had continued to advise him to avoid all physical exercise, and had told him he "should be like the bums in the pool room." He was convinced that he was unable to work or engage in any activity and had a fixed attitude of disability. The Minnesota Multiphasic Personality Inventory showed no change from the normal record of 17 months previously.

This case illustrates an instance in which the patient is handicapped not by his hypertension but by his attitude of disability, which unfortunately had been fostered by his local physician.

Discussion

Before any discussion of these observations, it is appropriate to recall the results of some of the long-term studies that have been made on hypertension.

King, Carlile and Blackford,[2] in 1942, reported on a ten-year to sixteen-year follow-up study of 481 patients aged forty to seventy years. They found that 27 per cent were living, and the average age at death in the others was sixty-two years. The average life expectancy after the discovery of hypertension was twenty years. A high diastolic blood pressure and evidence of cerebral, cardiac or renal damage indicate a higher mortality.

Palmer, Loofbourow and Doering,[3] in a follow-up study of eight years on patients treated by conventional medical therapy, found that the mortality was 22 per cent in Grade I, 47 per cent in Grade II, 78 per cent in Grade III and 94 per cent in Grade IV.

Burgess[4] reported on a group of 100 patients who were alive eight years after hypertension was found; the hypertension in this group was not rapidly progressive. These patients were followed at least eight years later; 47 were living, and 53 were dead. Of all patients, both living and dead, the duration of life was only four and one-tenth years less than the average life expectancy for the general population.

These figures indicate that the prognosis for hypertension is by no means necessarily unfavorable, particularly in Grades I and II without a high diastolic pressure, and without significant cardiac, renal or cerebral damage. Therefore, an attitude of acute anxiety and alarm whenever hypertension is discovered is not always appropriate for either the physician or the patient. Such a reaction on the part of the patient is understandable, particularly when one considers that the personality type is often prone to excessive anxiety and dependence, and that hypertension is a condition toward which a certain amount of anxiety is an appropriate reaction. That an attitude of undue alarm on the part of the physician is not only inappropriate but often harmful to the patient is the outstanding finding illustrated by these cases. What I have called secondary anxiety is often fostered either intentionally or unintentionally by the physician.

It is well known that patients with hypertension may be free from symptoms. Many patients in this series showed symptomatic improvement without change in the blood-pressure level, indicating that the symptoms are often the result of accompanying nervous reaction rather than of the increased blood pressure. Furthermore, the nervous reaction and the symptoms thereof are frequently the main cause of disability. Therefore, the importance of treating this nervous reaction is obvious, whether or not the blood pressure is affected thereby.

The treatment of the secondary anxiety is the first line of attack, and many of the cases illustrate symptomatic improvement when this is alleviated. Other patients show symptomatic improvement when specific conflicts are dealt with, or when an environmental situation is altered. Cases are reported in which both the symptoms and the blood-

pressure level vary with emotional and environmental situations. The value of reasonable mental and physical hygiene is illustrated by symptomatic improvement when such attitudes and habits are altered.

It cannot be concluded from this or any other study of which I am aware that psychotherapy can alter the eventual course or lower the mortality of hypertension. There is no long-term follow-up study of a sufficient number of patients with adequate controls. However, there are patients in this series who have had not only symptomatic improvement but also a definite reduction of blood pressure, apparently by psychotherapeutic means. In others, whose condition became worse, emotional and environmental factors seemed to be of importance. There is good evidence, therefore, that emotional factors are an aggravating influence on the course of hypertension. Though many other factors have a bearing on hypertension, the emotional element is often the important one to treat.

Connell,[5] in his study of 60 patients with essential hypertension in 1946, stressed the primary importance of neurogenic factors in the development of hypertension. He pointed out that permanent hypertension may develop with psychologic or autonomic nervous upsets. He considered the treatment of the anxiety, the patient's personality and adjustment most valuable.

Wolf and his associates,[6] in 1948, reported on the reaction to psychologic stress of 58 subjects with hypertension. They found that the subjects met threats with an attitude of restrained aggression and a vascular reaction of increased blood pressure and renal vasoconstriction.

These studies suggest that a vicious circle may be set up by the interaction of neurogenic and humoral influences, leading in time to progressive organic changes. Any means by which this circle can be interrupted or progression slowed seems to be worth while, and treatment of the emotional factors may be one means of attacking the problem.

The suggestions I would make on the basis of the patients studied are first to *avoid alarming the patient.* Frequent determinations of the blood pressure or the advice to give up all physical activity may produce almost as much anxiety in some patients as the statement that they may die by next week. Secondly, *reassurance and mental hygiene should be given.* By reassurance is meant the giving of a reasonable prognosis after any necessary study. It also means taking the time to determine what misconceptions and unreasonable fears the patient has about his condition, and attempting to correct them. Mental hygiene means the encouragement of a reasonable program of work, rest and recreation that is consistent with the patient's physical condition. It also means the encouragement of emotional expression to a reasonable degree in patients whose tendency it has been habitually to "hold things in." Thirdly, *the possibility of emotional trauma or conflict as a precipitating or aggravating factor should be considered.* The blood pressure may be very high at times of acute environmental or emotional stress, improving markedly when this stress is relieved. Whether or not the height of the blood pressure is affected, the symptoms are likely to be. Finally, *psychiatric management should be continued.* This most certainly does not mean that psychiatric treatment by a specialist is recommended except in cases of severe neuroses. It does mean that the physician caring for the hypertensive patient cannot always hope to influence him significantly in one visit. The patient may well benefit, however, from repeated reassurance, and from encouragement and guidance in seeking to modify his habits and attitudes. Personal problems may only be expressed after confidence is gained. Management of the emotional factors, along with medical treatment when the patient is seen from time to time, constitutes psychotherapy, and it is rarely necessary that this be done by a psychiatrist.

Summary

In a psychiatric follow-up study of 74 patients with hypertension one year or more after the initial examination, 15 of 18 patients treated by sympathectomy showed symptomatic improvement, 11 of 13 patients treated by psychotherapy showed symptomatic improvement, and 20 of 43 patients given reassurance alone showed symptomatic improvement.

Cases illustrating the role of emotional factors, particularly secondary anxiety, in the production of symptoms and aggravation of the condition are reported.

Principles of simple psychotherapy suggested include avoidance of alarm to the patient, reassurance and mental hygiene, consideration of the possibility of emotional trauma or conflict as a precipitating or aggravating factor and continuance of psychiatric management.

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INTESTINAL LIPODYSTROPHY (WHIPPLE'S DISEASE)*

Report of a Case

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AUTHENTIC reports of intestinal lipodystrophy, first recognized and described by Whipple[1] in 1907, have appeared so infrequently since then that the disease may well be classed among the rarer entities. The original description noted, during a period of over five years, arthritis, weight loss, secondary anemia, cough, diarrhea, abdominal distention, ankle swelling, dyspnea and a palpable mass in the right lower abdominal quadrant, with autopsy findings of deposits of fat and fatty acids in the intestinal wall and mesenteric lymph nodes. The actual number of similar cases reported in the intervening years has varied because not all have conformed strictly to the original criteria, although all possessed the common denominator of failure of fat transport from the small intestine along normal channels.

Full discussions of the subject may be found in the excellent reviews of Fitzgerald and Kinney[2] and Rosen and Rosen.[3] The former reported what they counted as the eighth case, and the latter the twelfth case on record, admitting that if all listed cases were included, theirs would be the nineteenth. Jones and Paulley[4] estimated that less than 25 cases had been reported up to 1949, listing those of Blumgart,[5] Fleischmann,[6] Jarcho,[7] Hill,[8] Korsch,[9] Boeck,[10] Reinhart and Wilson,[11] Pearse,[12] Amsterdam and Grayzel,[13] Oliver-Pascual et al.,[14] Sailer and McGann,[15] Apperly and Copley,[16] Pemberton and his associates,[17] Chapnik[18] and the 2 noted above. More recent reports are those of Newman and Pope,[19] Schutz, Benner and Christian[20] and Hendrix and his co-workers.[21]

I wish to add to the group the case of a patient under observation for two and a half years in whom the condition was recognized a year before death.

CASE REPORT

A 56-year-old man first came under observation in August, 1944, because of pains in the left elbow and both ankle joints that had persisted for 3 years in spite of a wide variety of treatment. At the onset most of the pain was in the lower back and was attributed to an osteoarthritis. Shortly thereafter, and for no known reason, he began to lose weight — a total of 40 pounds — in the next 3 years. The tonsils and several teeth had been removed within the 1st year, and each procedure was followed by an exacerbation of the arthritis. He had been treated with salicylates, intravenous injection of typhoid vaccine, thyroid substance, vitamin D, liver and iron injections, diathermy and some thirty injections of gold salts. An x-ray study of the gastrointestinal tract was reported as negative.

Physical examination revealed a large-framed, muscular man, weighing 174 pounds. The blood pressure was 120/80. There were no joint changes, but the right leg was swollen from the knee down, with numerous large, tortuous varicose veins. A traumatic cataract was present in the left eye. Studies of the blood showed a red-cell count of 4,260,000, with a hemoglobin of 77 per cent (Sahli), and a white-cell count of 17,700, with 82 per cent neutrophils, 16 per cent lymphocytes and 2 per cent eosinophils. The sedimentation rate was 44 mm. in 1 hour. The blood Kahn reaction was negative. The fasting blood sugar was 89 mg., and the uric acid 3.5 mg. per 100 cc. Agglutination tests for *Brucella abortus* were negative. Several urinalyses were normal.

A high ligation of the right saphenous vein was performed, and the leg swelling gradually decreased. There was improvement of joint pains during the next 8 months on treatment with salicylates and iron, and the weight increased by 10 pounds. Within a short time, however, weakness, anorexia, fleeting joint pains, slowly progressive weight loss and anemia developed. X-ray studies of the chest, gastrointestinal tract and gall bladder were negative, except for a small diverticulum in the second portion of the duodenum.

The patient was restudied in December, 1945, because he was not improving. Examination of the blood disclosed a red-cell count of 4,600,000, with a hemoglobin of 10.8 gm. per 100 cc., and a white-cell count of 6600, with 85 per cent neutrophils, 11 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. X-ray study of the chest now showed a prominent left ventricle, whereas that of the gastrointestinal tract remained unchanged. Gastric analysis demonstrated absolute achlorhydria.

During the course of the gastrointestinal study a mass believed to be in the pancreas was palpated once in the left upper abdomen outside the stomach but could not be felt subsequently. After many unsuccessful attempts to locate this mass, including retrograde pyelography, exploratory laparotomy was performed by Dr. W. D. Barrett on December 20. The spleen, liver and pancreas were normal, but the duodenum and jejunum were shiny gray and somewhat thickened. The mesentery had a similar color, was studded with enlarged lymph nodes and was markedly thickened, which was probably what had given the impression of a palpable mass. A lymph node removed for study (Fig. 1) showed chronic inflammation with a foreign-body reaction around lipid material — a change similar to that described by Whipple.[1] The patient made an uneventful recovery and was given 2.0 gm. (30 gr.) of bile salts daily in the hope of duplicating the experience of Pearse[12] in his successful management of a patient with a similar condition.

A persistent cough with copious expectoration developed soon after discharge from the hospital, but repeated sputum examination showed nothing remarkable. The blood cholesterol was 186 mg., and the nonprotein nitrogen 30 mg. per 100 cc. The icteric index was 4, and a stool analysis demonstrated 12.5 per cent total fats, with 11.1 per cent fatty acids and 0.13 per cent neutral fat. Examination of the blood revealed a red-cell count of 4,610,000, with a mean diameter of 8 microns and 12.5 gm of hemoglobin, and a white-cell count of 12,200, with 70 per cent segmented neutrophils, 6 per cent stab forms, 12 per cent lymphocytes, 3 per cent eosinophils, 2 per cent monocytes, 1 per cent basophils and 0.85 per cent reticulocytes. Fragility of the red cells was between 0.44 and 0.26 (normal, 0.44 to 0.32). The color index was 0.88, the hematocrit 46 per cent, the thrombocytes 391,000 per cubic millimeter, and the coagulation time 10 and the bleeding time 1½ minutes. Clot retraction and prothrombin were normal, and the icteric index was 1. The red cells showed only slight macrocytosis.

Weight loss and weakness continued, and the patient reported an occasional sudden, loose, voluminous, brown to yellow, foul stool. Pancreatic extract (Panteric tablets) was added to the bile salts, iron was still being taken, and he was given injections of crude and concentrated liver extract, all without effect. Six weeks after operation he noted

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that ingestion of any appreciable amount of fat produced marked flatulence and distress, followed by a loose, voluminous stool.

A detailed x-ray study of the small bowel showed definite delay in the progress of the barium and a distinctly abnormal pattern, some of the segments having very deep haustral markings and irregular barium distribution. There was some tendency for pooling in the mid-ileal segments, whereas some portions of the small bowel showed only a ribbon of barium. One segment in the right upper quadrant had a distinctly irregular appearance. One hour after the barium had been ingested it had reached the mid-ileal segments, but from there on there was definite delay in the progress to the cecum. At the end of 4½ hours the major portion of the barium was still in the small intestine, and only a trace had appeared in the large bowel (Fig. 2) These findings were compatible with the changes observed in idiopathic steatorrhea or severe avitaminosis.

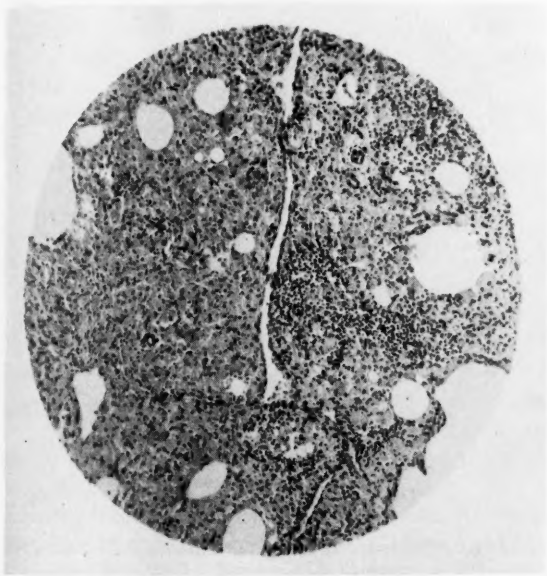

FIGURE 1. *Photomicrograph of Lymph Node Removed at Laparotomy, Showing Almost Complete Replacement by Lipid-Containing Cells.*

Little improvement occurred during the next few months. There was gradual weight loss, with increasing weakness. Loose, voluminous stools were now being passed once or twice daily and more frequently when any amount of fat was ingested. One and a half grams of choline citrate was added to the daily medication, and 15 mg. of folic acid was injected daily for a full month, without any benefit. Insulin in a dose of 5 units was then administered before each meal for a 2-month period, with only temporary improvement. The diarrhea became more persistent so that fat intake had to be reduced to a minimal level.

By September, 1946, the weight was down to 144 pounds —a loss of 30 pounds in 2 years. The hemoglobin was now down to 8.8 gm., and the red-cell count to 2,920,000. Additional treatment at this time consisted of 2 cc. of adrenocortical extract (Eschatin) intramuscularly daily for 1 week and 5 whole-blood transfusions of 500 cc. each over a period of 12 days. Repeated x-ray examination of the gastrointestinal tract and chest showed nothing new and the bones of the thorax were intact. Several urines were negative for Bence-Jones protein. The sternal bone marrow revealed no significant diagnostic pattern.

Additions to the medication for periods considered sufficient for evaluation consisted of 6 gm. of lecithin daily, dilute hydrochloric acid in divided doses, 5 mg. of synkamin daily and injections of large doses of vitamins A and D. Nothing seemed to retard the downward progress, and the diarrhea became more severe in spite of a low residue diet of 350 gm. of carbohydrate, 100 gm. of protein and 40 gm. fat, and frequent large doses of paregoric. In November daily feeding of a single minced hog pancreas dissected free of fat was started and continued for a 7-week period while several different brands of bile salts and pancreatic extract were tried.

In January, 1947, 2000 cc. of whole blood and 1500 cc. of plasma were given in an 8-day period, with little change in the general condition. At this time duodenal contents were aspirated from a healthy subject 3 hours after a high-fat meal, and 2 ounces of this mixed with 8 ounces of 20 per cent cream was instilled into the patient's duodenum. Diarrhea occurred promptly and lasted several hours. Soon afterward bile obtained by surgical drainage was instilled in 100-cc. portions twice daily by duodenal tube for a 10-day period, without effect. At the same time daily intramuscular injections of sterile sesame oil, starting with 2 cc. and increasing to 30 cc., were given for 11 days, and although the material seemed to be absorbed promptly, no benefit resulted. Finally, a series of 6 500-cc. transfusions of whole blood obtained from suitable donors 3 hours after ingestion of a meal containing 400 gm. of fat was given, but still without results. In spite of all efforts the patient continued to fail, dying on February 17.

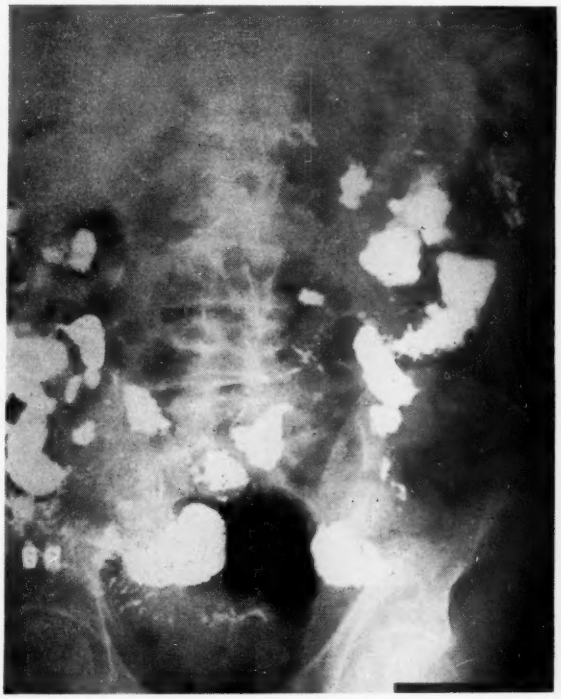

FIGURE 2. *Roentgenogram, Showing Puddling of Barium in the Small Intestine.*

At autopsy the gross anatomic findings consisted of generalized emaciation, contraction and irregularity of the right pupil and dental caries. There was a bilateral hemothorax and minimal bilateral pulmonary edema. The coronary arteries and aorta showed minimal atherosclerosis and adhesive and fibrinous pericarditis. The thoracic duct was patent. Mesenteric lymphadenopathy was widespread. The mesentery was thickened and greasy gray. In the digestive tract there was loss of external striation of the small bowel, with thickening of the wall and a greasy-gray appearance. There were scattered ulcerations of the mucosa with some

hemorrhage. The brain showed fine granulations on its surface.

On microscopical examination sections of the heart revealed many scattered foci in the interstitial tissue composed of lymphocytes, a few macrophages, giant cells with centrally and peripherally placed nuclei and some fibroblasts. Some foci consisted of perivascular collections of lymphocytes. The epicardium was covered by fibrin and infiltrated with lymphocytes. There was some proliferation of fibroblasts and young capillaries. There was marked internal thickening and hyalinization of the coronary arteries, with deposition of calcium (Fig. 3).

Microscopical sections of the lungs disclosed patchy areas of atelectasis and emphysema. Deposits of anthracotic pigment were present. Some alveoli contained macrophages, with brown-staining pigment. A few alveoli contained small masses of pink-staining fibrinoid material.

There were no notable morphologic alterations in the liver or adrenal glands.

Sections of the spleen revealed hyaline perisplenitis but no alteration of pulp.

In one kidney a few glomeruli had been replaced by hyalin, with atrophy of the corresponding tubules. The medium-sized vessels of the kidney were distended with red cells.

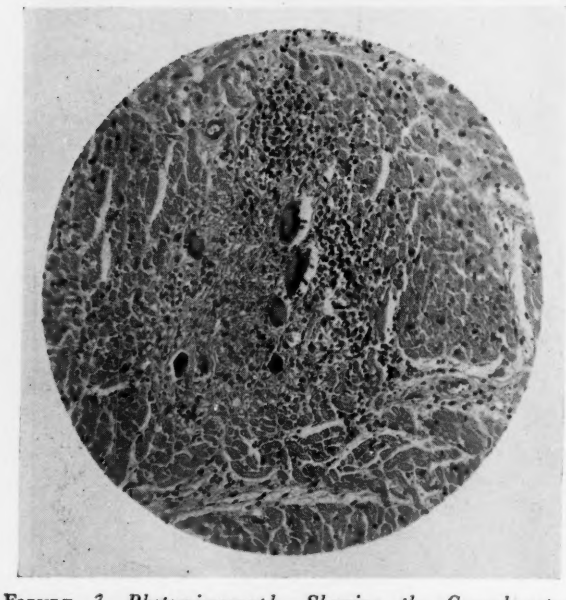

FIGURE 3. *Photomicrograph, Showing the Granulomatous Lesion in the Myocardium.*

The testes demonstrated no notable morphologic alterations.

In the pancreas slight edema was present through all portions of the microscopical sections. The ducts were dilated, and a few medium-sized, enlarged ducts showed slight desquamation of the lining epithelium. There was no evidence of fibrosis. In all other aspects the organ was histologically normal. The entire pancreas was removed and analyzed for its insulin, amylase, lipase and trypsin content. All were present in normal amounts.

Microscopic section of the small intestine revealed the villi to be increased in size, with numerous foam cells in the substantia propria. In most areas the epithelium was present, but in some it was denuded, possibly owing to expansion of the villi by the accumulation of foam cells. There were dilated endothelial-lined spaces in the substantia propria, submucosa and serosa. Most spaces were empty, but some were filled with pale, pink-staining material. Most of these spaces were partially surrounded by multinucleated cells. Special Sudan stains showed the foam cells in the substantia propria and the spaces in the submucosa and serosa to be brilliantly stained. Fat droplets were seen lying free in the serosa (Fig. 4).

Sections of the lymph nodes revealed many large spaces near the hilus that were lying by multinucleated cells. Some spaces were empty, whereas others were filled with pink-staining material. The sinuses were filled with foam cells pressing the lymphocytic cords. Special Sudan stains revealed the foam cells in the dilated spaces to be stained a brilliant red.

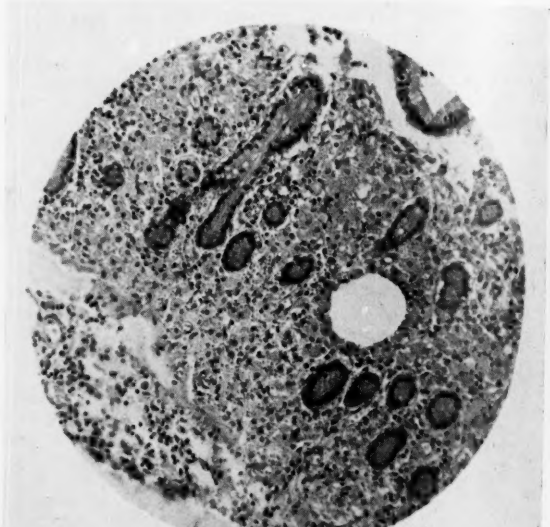

FIGURE 4. *Photomicrograph of the Intestinal Mucosa Filled with Lipid-Containing Cells.*

Microscopical study of the sections of the brain showed the vessels, including the small capillaries, to be distended with red cells. There were no extravasated red cells.

The microscopical diagnoses were intestinal lipodystrophy (Whipple's disease) involving the small intestine, mesentery and lymph nodes; fibrinous pericarditis; granulomatous foci in the myocardium; and hyaline perisplenitis.

DISCUSSION

There is close similarity between the clinical evidence presented above and that brought out by Whipple[1] in his original description of this peculiar entity. This fifty-six year-old patient had arthritis, anemia, weight loss, debility and diarrhea, with an increase of fat in the stools, and at autopsy showed a pericarditis and deposits of fat and fatty acids in the small bowel and mesenteric lymph nodes. Discovery of the condition approximately a year before death afforded the opportunity to make a number of observations, the following being the most significant.

The blood cholesterol level dropped in the course of a year from 186 to 55 mg. per 100 cc. When the disturbance was at its height the alkaline phosphatase was 9.0 units, the acid phosphatase 4.1 units, and the blood amylase 84 mg.

per 100 cc., and the lipase the equivalent of 0.1 cc. of sodium hydroxide. The cephalin flocculation was negative at twenty-four and ++ at forty-eight hours, whereas the hippuric acid test was within normal limits.

Shortly after operation the total blood protein was 6.84 gm. per 100 cc., with 2.78 gm. of albumin and 4.06 gm. of globulin (0.68:1), and shortly before death it was 4.28 gm. with 2.15 gm. of albumin and 2.13 gm. of globulin (1:1).

An oral glucose-tolerance test using 100 gm. glucose showed a fasting level of 92 mg. per 100 cc., 175 mg. at forty-five minutes, 186 mg. at two hours and 104 mg. at three hours.

Gastric analysis demonstrated absolute achlorhydria on two occasions.

A year before death stool analysis for fats showed 12.5 per cent total fats (dry weight) with 11.1 per cent fatty acids and 0.13 per cent neutral fats. Eleven months later the fat content had increased to 34 per cent.

A fat-tolerance test was performed by the administration of 400 gm. of fats in a milk and cream mixture. The fasting blood lipid level was 500 mg. per 100 cc. At three hours it was 340 mg., at six hours 380 mg. and at the end of fifteen hours 480 mg. Severe diarrhea began three hours after the meal.

On the therapeutic side, in addition to iron, salicylates, hydrochloric acid and vitamins A, D and K, various bile salts were tried from the time the diagnosis was first made. These had been used with success by Pearse[12] but failed to evoke a response in this patient.

Insulin was tried because it seemed well established from the work of Stetten and Boxer,[22] MacKay and Drury,[23] Tuerkischer and Wertheimer[24] and Best[25] that it plays an important role in the formation of fats from carbohydrates. Choline and lecithin were also tried in an attempt to promote fat transport.[26] Adrenocortical extract was given because it had been observed[27] that adrenalectomy in animals impairs the absorption of fat. Folic acid and crude as well as concentrated liver extract were administered parenterally because of the resemblance of this case to the sprue syndrome.

Plasma and blood transfusions were given frequently, and several of the latter were purposely obtained from donors who had had a high-fat meal three or four hours before bleeding.

Commercial pancreatic extracts were tried for an extended period, and lipocaic would have been tried but it was not obtainable. In its place, a raw minced hog pancreas was given daily for seven weeks.

On one occasion duodenal contents were aspirated from a healthy subject three hours after a high-fat meal, and 2 ounces of this material was mixed with 8 ounces of 20 per cent cream and instilled into the duodenum of the patient. This was promptly followed by a severe diarrhea that lasted several hours.

At another time bile obtained by surgical drainage from another patient was fed by tube in 100-cc. quantities twice daily for ten days, without notable effect.

Finally, in the belief that intravenously administered fat emulsions might be of help, an emulsion of olive oil was prepared, with globules 2 microns in diameter. Rabbits withstood sizable injections of this emulsion, but since there was no assurance that larger globules were not also present the material was not used.

A number of explanations for the disturbed fat metabolism in intestinal lipodystrophy have been advanced, but proof of their validity is still lacking. In the patient described above, whose pancreas was apparently normal, the failure of insulin, bile salts, human bile, duodenal contents, pancreatic extracts and raw hog pancreas to exert a favorable influence indicate that there was no lack of any duodenal substance essential for the proper preparation of fat preceding its passage into the intestinal mucosa. It seems, then, that faulty interaction within the mucosal cell, through either absence of some key substance or the influence of a toxic agent resulting from chronic inflammation, allowed incompletely prepared fat to pass through and to act as a foreign body, with cumulative packing into the surrounding lymph channels and lymph nodes and ultimate blockage of lacteals.

Summary

A case of intestinal lipodystrophy that fulfilled the criteria set forth in Whipple's original description is presented.

With the diagnosis established a year before death there was opportunity to make a number of observations that pointed toward defective metabolism in the cells of the intestinal mucosa as the causative factor.

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LIQUOR ADULTERATED WITH LYE AS A CAUSE OF DYSPHAGIA AND STRICTURE OF THE ESOPHAGUS*

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IN THE literature on corrosion and stricture of the esophagus I remember reading about an alcoholic patient who for years had been in the habit of drinking whisky straight and who finally cast up the whole wall of his esophagus. Now and then, casting up of "Ausgusse" of the esophagus happens specifically in patients with lye corrosion one to three weeks after the accident. In the case described above the phenomenon was explained as being due to use of too-concentrated alcohol. I have never observed anyone to have paid attention to the following possible cause of corrosion.

The Finnish man generally knows that weak spirits can be fortified with lye (recently DDT has also been used for the same purpose). I have heard that during prohibition (before 1932) smugglers sometimes resorted to this method of adulteration and made 2 liters of spirits out of 1. According to the Gallup estimation made in 1948, on the average 10 illicit distilleries existed per parish — that is, a total of 6000 in the whole country. In consequence of defective means employed in illicit distilleries the "moonshine" often was not strong enough in alcoholic content. Consequently it is no wonder that the moonshiner wished to "improve" his product. The lye generally used for household purposes constitutes a most suitable admixture: it is cheap, it readily dissolves into water and alcohol, it is colorless and odorless and, what is most important, it gives a pungent taste. The sweet taste of highly diluted lye (as well as that of alcohol) depends on the presence of OH ions, the threshold value being 0.006 to 0.009 gm. of ions per liter.[1] I myself have tasted lye solution and ascertained it to bite my tongue just as a strong solution of spirits does. If approximately a 40 per cent aqueous solution of alcohol is diluted with an equal amount of 1 per cent aqueous solution of sodium hydroxide a 0.5 per cent lye solution results that bites the tongue as quickly and sharply as 96 per cent alcohol. That adulteration of the kind described is truly used is proved by the existence of a method for detecting the falsification. This method is relatively popular among the middleaged: the alcohol is poured onto the hands, and if, when they are rubbed together, they become slippery and foam develops the liquor is adulterated with lye.

Animal tests show that a 0.5 to 1 per cent lye solution is capable of corroding the mucous membranes of the esophagus and the stomach.[2] Some of the cases analyzed by me are indicative of the fact that for children only a mouthful of lye solution whose concentration is not even 0.5 per cent is sufficient to produce a deleterious effect.[3] Hence, to the adulterator lye is advantageous in that a lye solution whose concentration does not exceed the threshold value for bringing about corrosion mixed with 40 per cent alcohol can provide a drink that, so far as taste is concerned, corresponds to strong liquor. Whether or not the adulterator always stays beneath 0.5 per cent solutions is another matter.

At the Oto-Laryngological Clinic of the University of Helsinki some cases of corrosion have been treated that, with great certainty, were due to liquor adulterated with lye.

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Case Report

Case 1. A 65-year-old laborer (No. 871/49) on September 15, 1949, drank from a bottle at his neighbor's illicit distillery brown liquid that was supposed to be and smelt like moonshine. The liquor burned very much, and therefore the patient drank little of it. The skin from his lips and mouth was burned. He arrived at the Oto-Laryngological Clinic after 4 weeks because of difficulties in swallowing.

The mucous membrane lining the palate and pharynx was thin and scarred in various places, and the region of the isthmus faucium bled readily. On x-ray examination the patient had difficulty in swallowing both soupy and pulpy contrast medium. He vomited immediately everything he drank. In a very narrow channel the contrast medium ran into the stomach. The mucous membrane of the esophagus gave the impression of being irregular. After 5 weeks bougies No. 13-19 (Charr.) passed the esophagus with difficulty.

Case 2. A 70-year-old laborer (No. 863/49) had been offered moonshine in June, 1949, by a tramp, who drank some of it himself. While the patient was drinking the burning sensation in the mouth was not more pronounced than usual but after a couple of days he began to vomit. The matter vomited was slimy and bloody, and the tongue sore. Since then he had been able to eat liquid food only and was emaciated. After 3 months a rural physician sent the patient to Helsinki to the Surgical Hospital suspecting carcinoma of the esophagus. From there the patient was sent to the Oto-Laryngological Clinic, the diagnosis being suspected carcinoma of the esophagus and stricture due to ingestion of a corrosive, with the remark that the roentgenologist suspected stricture but that the patient denied drinking lye.

Examination showed obvious scars and atrophy of the mucous membranes in the palate and the back wall of the pharynx; the uvula and tonsils were congested with blood. At a distance of 29 cm. the esophagus contracted into a concentric canal measuring 3 or 4 mm. in diameter. The mucous membrane was smooth, reddish, under cover of a gray layer of pus and bleeding readily from parts near the stricture. Biopsy of the bleeding tissue demonstrated chronic inflammation. The x-ray report was as follows:

> Near the bifurcation the canal contracts suddenly into a rough-walled tube, 2 or 3 mm. thick, and continues thus for 12 cm. Roentgenologically, the appearance gives the impression of a stricture due to old inflammatory changes. The diagnosis is questionable stricture with carcinoma of the esophagus.

Bougies No. 15-17 (Charr.) passed the esophagus with difficulty.

Case 3. A 54-year-old laborer (No. 5/49 OPD) drank for 2 successive days in November, 1948. When the liquor bought from a shop came to an end more was obtained from an illegal source. The patient remembered events indistinctly, but recalled that on the 3rd day, while he was drinking coffee, his mouth and esophagus had felt rough and that subsequently for 3 weeks only souplike food went down. His status was continuously slightly improving, but after 2 months he was capable of swallowing only soup-like and porridge-like food. Roentgenologic examination revealed conical, rigid stenosis of the esophagus above the cardia. Esophagoscopy after 2½ months showed the mucous membrane of the esophagus to be swollen and red, and the lumen dilated. The mucous membrane in the region of the cardia was exceptionally thick and firmer than usual without normal folds. Bougie No. 29 passed through the cardia with slight difficulty.

These 3 cases occurred approximately within half a year, and all the patients connected the onset of dysphagia with liquor drinking. Neither the patient nor his doctor believed that the basic cause was lye.

Lye used for adulterating liquor explains some of the cases of dysphagia and stricture of hitherto unknown causes.

Case 4. A man born in 1886 (No. 517/26) had been hospitalized at the Oto-Laryngological Clinic several times since 1926 for treatment of dysphagia dating back to 1925. Despite various attempts at finding the cause of the stricture it remained unsolved. In January, 1949, the patient was hospitalized again (examination revealing malignant transformation, carcinoma keratinosum, of the esophagus developing on basis of stricture). Then he stated that before difficulties in swallowing had appeared he had been an incurable alcoholic addict whose drinking periods lasted for months. When the Prohibition Law came into force (1919) he often drank undiluted liquor bought from smugglers.

Case 5. A man born in 1892, (No. 207/49 OPD, a poorhouse inmate, was a chronic alcoholic addict. On September 10, 1949, he stated that for about 1 year food had lodged in the esophagus. Now only liquid food went down, and he was emaciated. Roentgenographic examination showed the esophagus to be slightly dilated at the level of the aorta. In the bifurcation region a fairly sudden narrowing occurred, the mucous membrane at this point not being quite smooth. Caudal to the bifurcation the esophagus contracted slightly. The roentgenographic diagnosis was questionable carcinoma of the esophagus. Esophagoscopy disclosed circular narrowing 32 cm. from the upper teeth. The mucous membrane was exceedingly thick, with folds. The changes appeared like esophagitis and not like carcinoma. On biopsy there were no signs of malignant changes or specific inflammation.

In addition to these 5 cases the material at the Oto-Laryngological Clinic (consisting of a total of 420 cases of corrosion and stricture) comprises 25 cases hitherto explained by mistaking of a lye bottle for an alcohol bottle. In at least 11 of these cases the circumstances at the moment of the accident can be construed as cases in which alcohol was deliberately adulterated with lye, too great an amount of lye being added by mistake or ignorance, rather than cases in which a lye bottle has accidentally been mistaken for an alcohol bottle. In other words, in many of these cases a good friend offered drinks straight from a liquor bottle bought from a smuggler or moonshiner.

Of all the patients who have taken lye and received treatment at the Oto-Laryngological Clinic four fifths suffer from achylia, and in the majority anemia develops.[3] The gastric-acid secretion and blood changes in the cases reported above differed in no way from those in other cases of lye corrosion.

The cases of cicatricial stenosis of the esophagus are almost solely caused by caustic alkalis and strong acids. However, according to Vinson,[4] the etiology of 10 per cent of cases of stricture of the esophagus remains unsolved.

The case referred to in the beginning of this paper does not provide sufficient evidence that alcohol, taken in concentrated form, is capable of causing such deep changes comparable to colliquation as to lead to stricture of the esophagus. According to the literature and according to tests made in Finland,[5] DDT (used besides lye in adulterating liquor) is also incapable of injuring the mucous membrane. Conversely, the use of lye in adulterating liquor provides an explanation for cause of dysphagia, stricture of the esophagus, achylia and anemia in some cases. Carcinoma of the esophagus

has been regarded by various investigators as an illness resulting from chronic alcoholism, but experts on chronic alcoholism[6, 7] arrive at the conclusion that chronic alcoholism plays no part in the development of the disease. On the other hand, Kiviranta[8] shows that in thirty years carcinoma of the esophagus develops in approximately a third of patients with lye corrosion.

SUMMARY

Cases in which caustic soda used for adulterating liquor (a method generally known in Finland) apparently caused dysphagia and stricture of the esophagus, as well as achylia and anemia, are reported. The etiology described may be hitherto unknown in medical literature.

Kuusitie 3B

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MEDICAL PROGRESS

VITAMIN B_{12} AND PERNICIOUS ANEMIA (Concluded)*

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Vitamin B_{12} and Growth Factors for Rats

Just as the hen's diet affects the chick's requirement for growth factors, so the diet fed to impregnated rats influences the growth factors needed by the litters. When weanling rats of depleted dams are fed casein extracted with hot alcohol they fail to grow.[79] The growth factor is found in commercial casein, in variable amounts in "vitamin-free" casein, and in large amounts in commercial liver extracts. Milk, skimmed milk, cheese, beef and pork muscle contain this factor. Egg yolk contains variable amounts of the factor, depending on the hens' diet.[80] Although the size and birth weights of rat litters from dams fed a diet in which soybean meal constitutes the source of protein are uninfluenced by vitamin B_{12} supplements, the twenty-eight-day weights of young born of dams receiving vitamin B_{12} were 50 per cent higher than those of the controls. The former continued to grow well during the second month and were only slightly smaller at three months than the young born of deficient dams but supplemented with vitamin B_{12} after birth. As might have been anticipated, the best growth was exhibited by the young supplemented with vitamin B_{12} born of dams similarly supplemented. These data indicate that vitamin B_{12} is stored by the young during gestation or suckling, or both.[81]

Rats receiving thyroid substance and rations devoid of animal protein fail to grow properly. Vitamin B_{12} is equally effective orally and by injection in counteracting this growth retardation.[82] Similar growth retardation occurs in animals receiving iodinated casein and is correctable by whole liver, liver extracts high in antipernicious-anemia activity or vitamin B_{12}.[83] However, more than one "anti-thyrotoxic" factor may be involved since Ershoff[84] found that the addition of vitamin B_{12} to thyroid-fed rats receiving purified rations failed to re-establish growth but that a water-insoluble liver fraction was effective.

Frost et al.[85] have devised an assay method for vitamin B_{12} involving a diet devoid of vitamin B_{12} but containing iodinated casein, and sulfaguanidine to inhibit intestinal synthesis of vitamin B_{12}. They found the vitamin equally effective orally and by injection and observed no difference between adding the vitamin to the diet and administering it alone in single or multiple doses. They observed a good correlation between the microbiologic and rat assays as applied to injectable liver extracts.

Hartman and his associates[54, 55] found that certain young rats failed to grow well on a purified diet unless fed feces of rats that were growing adequately. It appeared that succinylsulfathiazole (Sulfasuxidine) inhibited the intestinal synthesis of this growth factor and that a high level of riboflavin in the diet favored synthesis. The same workers also showed[86] that young rats deficient in vitamin B_{12} and receiving 25 per cent dietary protein doubled their growth when vitamin B_{12} was added; those receiving 45 per cent dietary protein tripled growth; those getting 65 per cent protein showed more than a tenfold increase, sug-

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gesting that vitamin B_{12} plays a fundamental role in the capacity of the normal rat to utilize protein.

A curious syndrome called acute uremia of the newborn, which occurs when rat dams are fed a soybean protein preparation and DL-methionine as the sole source of amino acids, can be prevented by injection of vitamin B_{12} into the newborn.[87]

Vitamin B_{12} and Growth Factors for Other Animals

Liver contains a growth factor that counteracts the growth-retarding effect of thyroid-active materials in mice.[88] A vitamin B_{12} concentrate (not pure) promoted growth in weanling pigs fed a diet solely of vegetable origin,[89] and c stalline vitamin B_{12} is as effective as liver extract in this regard.[90]

Microbiologic Assay

The use of *L. lactis* (Dorner) for the assay of the vitamin B_{12} content of various substances, including liver extracts offered for the treatment of pernicious anemia appeared very promising at first. However, Shorb and Briggs[91] soon showed that dissociation occurs in cultures of this organism and that some of the variants may not require vitamin B_{12} for growth. They also found that a number of substances often present in materials to be tested had, in sufficient concentration, growth-inhibitory effects. These included sodium chloride, folic acid, para-amino benzoic acid, serine and xanthine. Subsequently,[92] it was shown that *L. lactis* did not grow in the absence of carbon dioxide and in the presence of 100 per cent carbon dioxide exhibited maximal growth in the entire absence of vitamin B_{12}. Small concentrations of carbon dioxide (1 to 5 per cent) in an atmosphere of nitrogen also permitted maximal growth without vitamin B_{12}. Increasing the aeration of the medium increased the amount of vitamin B_{12} required for maximum growth, whereas reducing substances (ascorbic acid, cysteine and so forth) that lower the oxidation potential of the medium eliminate the vitamin B_{12} requirement.[92, 93] Oxidizing agents inhibit *L. lactis* growth but can be overcome with vitamin B_{12}. However, in other instances it appears that growth occurs in the absence of reducing substances, vitamin B_{12} or any other known factors,[94] and hence the use of *L. lactis* growth as an assay method cannot be considered satisfactory.

Hoffmann et al.[95] noted that *Lactobacillus leichmannii* 313 exhibited growth responses to the anti-pernicious-anemia factor. However, by employing chromatographic separation, Winsten and Eigen[96] found three alternate factors that replaced vitamin B_{12} for the growth of this organism, which does not exhibit dissociation.[97]

Euglena has also been employed in assays for vitamin B_{12} activity,[98] but whether this method will be wholly satisfactory cannot yet be stated.

Leuconostoc citrovorum 8081 has been extensively studied. Although liver extracts potent in pernicious anemia are effective growth stimulants for this micro-organism, pure vitamin B_{12} is inert.[99] Assay of liver preparations with this organism generally differ significantly from assays on patients, or with *L. lactis*, the chick or the rat.[100]

It thus appears that at the time of writing *L. lactis* assay for vitamin B_{12} activity is a valuable exploratory tool, but that assays by chick or rat growth may not necessarily agree with microbiologic methods.

Role of Vitamin B_{12} in the Synthesis of Nucleic Acid

There is now considerable evidence that pteroylglutamic acid functions in the biosynthesis of purines and thymine or their equivalents.[101] For example, thymine or thymidine will replace pteroylglutamic acid as a growth factor for *Streptococcus faecalis R*, if either adenine or guanine is present in the medium.[102, 103] Thymine produces positive hematopoietic effects in pernicious anemia.[104] However, neither thymine alone or with adenine sulfate or adenosine nor thymine and adenine as thymus nucleic acid can replace pteroylglutamic acid in weanling rats receiving succinylsulfathiazole.[105] Further, thymine can substitute only partially for the pteroylglutamic acid requirement of *L. leichmannii*.[103, 106] The fact that five thousand times as much thymine as pteroylglutamic is required for the growth of *S. fecalis R* has led to the hypothesis that the latter functions directly or indirectly as a coenzyme in the synthesis of thymine or related compounds.

The fact that thymidine (thymine desoxyriboside) will replace vitamin B_{12} for the growth of *L. lactis*, although thymine itself is inactive[106-108] has led to the hypothesis that vitamin B_{12} serves in the biosynthesis of thymidine in a fashion similar to that of pteroylglutamic acid in the synthesis of thymine. Thymidine will replace vitamin B_{12} for *L. leichmannii* when ten thousand to twenty-four thousand times as much of the former is present in the medium.[103, 109] In addition, there are at least three other unidentified growth factors that will replace thymidine or vitamin B_{12} for this organism.[96]

It is of interest that vitamin B_{12} causes an increase in phosphorus uptake of *L. leichmannii*, particularly in the desoxyribonucleic acid fraction.[110] It appears that thymidine is not specifically required by at least 11 of 13 lactic acid bacilli studied by Kitay, McNutt and Snell,[111] since they found the desoxyribosides of adenine, hypoxanthine or cytosine equally effective, and desoxyribonucleic acid active for many of these organisms. However, a hydrolysate of guanine desoxyribose prepared to liberate free desoxyribose was inactive. The hypothesis suggested is that these desoxyribosides function by permitting the synthesis of desoxyribonucleic acid, which may also be permitted by vitamin B_{12} by an

independent process. Certainly, it is clear that guanine desoxyriboside will replace thymidine for three strains of thermobacteria, but vitamin B_{12} will not replace either for *Tuberculomyces acidophilus* R26.[112] *Lactobacillus bifidus* requires a desoxyriboside (either guanine or thymine) or desoxyribonucleic acid, which is not replaceable by vitamin B_{12}, thymine or ribonucleic acid.[113] Furthermore, it has been shown that thymidine is active in reversing the growth inhibition of *Leuconostoc citrovorum* 8081 produced by 4-aminopteroylglutamic acid, whereas vitamin B_{12} is completely ineffective.[114]

Conversely, in patients with pernicious anemia, Reisner and West[115] and Ungley[116] have been unable to demonstrate erythropoietic effects of thymidine injected in doses as high as 150 mg. although 1 microgm. of vitamin B_{12} daily subsequently produced satisfactory remissions. Slight increases of reticulocytes were observed, but no increases in red blood cells. However, Hausmann[51] has made the following statement:

> A highly purified concentrate of thymidine, free of vitamin B_{12} and folic acid, was prepared from purified liver extracts. In one patient with pernicious anemia where altogether 2 g. was given, after only 1 g. (administered intramuscularly in daily doses of 100-200 mg.) the megaloblastic marrow was restored to normoblastic and the reticulocytes rose to 17.2% with a subsequent increase of erythrocytes from an initial 2,400,000 per c.mm. to 3,200,000 per c.mm. within two weeks. A second case reacted in a similar way.

No further data are given.

The basophilic staining properties of normal liver parenchymal cells are attributed to the presence of ribonucleic acid compounds. When soybean oil meal is the sole source of protein in the diet of rats, liver basophilia disappears. Vitamin B_{12} or liver extracts prevent this disappearance.[117] Small doses of carbon tetrachloride deplete the ribonucleic content of the central lobular liver cells without producing other evidence of liver damage. The administration of vitamin B_{12} inhibits this depletion[118] and also diminishes the degree of both fatty metamorphosis and ribonucleic acid depletion produced by larger doses of carbon tetrachloride.[119]

Other Effects of Vitamin B_{12} on Animals

Weanling rats fed a basal diet containing only 0.04 per cent choline chloride grow poorly, and all succumb with a hemorrhagic renal syndrome. If 30 microgm. of vitamin B_{12} per kilogram of diet is added, growth is improved, and only half the animals develop the renal syndrome. The same amount of vitamin B_{12} added to diets with low levels of DL-methionine similarly reduces renal damage from 100 per cent to 25 per cent or less.[120] The choline requirement of the chick may be reduced to a sixth by vitamin B_{12}.[121, 122] There is evidence that a vitamin B_{12} concentrate containing amounts of choline and methionine that would be ineffective alone had lipotropic effects in rats similar to those observed with liver extracts.[123]

Pteroylglutamic acid deficiency in the chick leads to an increase in D-amino acid oxidase and xanthine oxidase. When vitamin B_{12} is added there is a further increase in D-amino acid oxidase[124] but not in xanthine oxidase.

Both liver extract and pteroylglutamic acid have been noted to reduce the toxicity of glycine in rats, the former having less effect, but both together being most effective.[125]

Pteroylglutamic acid is essential for growth of Rous-tumor implants in young chicks. Vitamin B_{12} does not completely replace folic acid, but when both substances are given the tumors attain great size.[126]

Effects of Vitamin B_{12} in Pernicious Anemia

Vitamin B_{12} is as effective as potent liver extracts on all the manifestations of pernicious anemia: hematopoietic,[38, 42, 127-136] gastrointestinal[34, 129-131, 137] and neurologic.[128-130, 133, 135, 138-140] As noted above, like liver extract, it is far more potent by parenteral injection than orally.[132, 136, 141-143] Sensitization has not been reported. There is no evidence that vitamin B_{12} has any beneficial effects in pernicious anemia that are not also found to follow the administration of potent liver extract.

The report that the response of the red blood cells in pernicious anemia is not as satisfactory after vitamin B_{12} therapy as after liver extract[144] appears unverified. In fact Ungley's[130] recent report definitely contradicts this claim, as do data in many of the references cited above.

It may be added that, although the hematologic picture and bone marrow of the adequately treated patient return to complete normality and although glossitis and atrophy of the mucous membrane of the tongue disappear and great improvement in neurologic manifestations may occur, gastric achylia remains and *long-standing neurologic signs* (presumably due to anatomic degeneration) are rarely reversible.[145]

Effect of Vitamin B_{12} on Related Macrocytic Anemias

Evidence presented by Wills and Evans[146] and Davis and Davidson[147] suggested that purified liver extracts, potent in the treatment of Addisonian pernicious anemia, were not effective in certain cases of pernicious anemia of pregnancy and were probably ineffective in certain other macrocytic anemias, which nevertheless responded to crude liver preparations or folic acid. Watson and Castle[148] corroborated these observations and concluded that, although the blood picture and bone marrow were morphologically similar to those in Addisonian pernicious anemia, the deficiency was of a different substance than the antipernicious-anemia factor. This material they termed the Wills factor, in recognition of the work of Lucy Wills,[149] who had

made the first experimental observations in this field. Davidson and Girdwood[150] have also reported cases of megaloblastic anemia that failed to respond to purified liver extracts but showed at least partial responses to "proteolyzed liver extract" and to pteroylglutamic acid. Recently, Day, Hall and Pease[151] reported the case of a patient with macrocytic anemia of pregnancy who was refractory to treatment with vitamin B_{12} but who responded at once to the administration of folic acid. Ungley[42] has recorded that one patient with macrocytic anemia of pregnancy did not respond to 65 microgm. of vitamin B_{12} although she did to 2.5 mg. of folic acid daily. A similar case has recently been reported of a patient who failed to respond to 10 microgm. of vitamin B_{12b} although subsequently undergoing remission with folic acid therapy.[48]

Luhby[152] reported the cases of 3 infants with "megaloblastic anemia of infancy" who failed to respond to 100 or more microgm. of vitamin B_{12} and who subsequently had remissions with pteroylglutamic acid or dietary therapy, or both. On the other hand, McPherson et al.[153, 154] have reported complete hematologic responses with a few micrograms of vitamin B_{12} in 2 apparently similar cases, and Davis and his co-workers[155] in a six-year-old child. Woodruff and his associates[156] have treated 5 infants with megaloblastic anemia with vitamin B_{12}. Three responded. Two failed to respond but then underwent remission when pteroylglutamic acid was administered.[156]

Spies and his colleagues,[131, 132, 137, 157-159] in a series of papers, reported the successful treatment of at least 14 cases of tropical sprue, 2 cases of nontropical sprue, and 17 cases of nutritional macrocytic anemia with parenterally administered vitamin B_{12}, and Patel,[160] of Bombay, treated 2 patients with characteristic tropical macrocytic anemia with 80 microgm. of Lester Smith's antipernicious-anemia factor and in each case obtained a prompt and satisfactory reticulocyte response, together with a return of the megaloblastic bone marrow to normal and a rise in red cells and hemoglobin.

At the moment, however, the question of what factors other than vitamin B_{12} are involved in tropical macrocytic anemia must be held *sub judice*, although the evidence that vitamin B_{12} is either not involved or, at least, is not the only deficiency involved in some cases of macrocytic anemia of pregnancy and megaloblastic anemia of infancy appears definite. These may resemble the macrocytic anemia that may be induced in rats by the production of a blind loop of intestine in which the direction of peristalsis is toward the blind end.[161] It responds to the administration of pteroylglutamic acid but not to purified liver extract or vitamin B_{12}.[162]

Other Effects of Vitamin B_{12} in Man

Forty micrograms of vitamin B_{12} had no effect on the white blood cells of a normal man in contrast to their rise after the injection of 10 cc. of commercial liver extract.[163]

Improved growth was noted in malnourished children given 10 microgm. of vitamin B_{12} orally daily. The most dramatic effects were noted in a boy who spontaneously recovered from asthma.[164]

In a letter written from New York to the editor of the *Lancet*, unequivocal diuretic effects were reported after the injection of 45 to 75 microgm. of vitamin B_{12} in 11 of 15 subjects. The 11 included 3 with chronic glomerulonephritis, 4 with pernicious anemia, 1 with cardiac decompensation and 3 volunteers. Two other volunteers and 2 patients with heart failure showed no response.[165]

Of considerable interest is the observation of Bean and his associates[166, 167] that in 4 patients with painful neuropathy associated with alcoholism and nutritional deficiency, the intramuscular injection of 15 microgm. of vitamin B_{12} was followed by relief of pain within an hour, whereas no effect was noted in 11 patients with painful neurologic conditions not associated with nutritional deficiency. Although the belief that thiamine deficiency results in the neuropathy of beriberi has been questioned,[168, 169] little study has been given this problem in recent years.

Relation to the Extrinsic Factor of Castle

The observation, made many years ago, that the potency of whole liver or active liver extracts could be further increased by the simultaneous oral administration of normal human gastric juice was interpreted to mean that, in addition to the antipernicious-anemia principle, extrinsic factor was present. It was assumed that the latter was acted upon by the intrinsic factor of the normal gastric juice added and that eventually the reaction led to the elaboration of additional antipernicious-anemia material.

The observation that vitamin B_{12} is more effective by injection than by mouth indicated that this material either was destroyed in the gastrointestinal tract or was incompletely absorbed. However, the finding of Bethell, Meyers and Neligh[170] that the feces of patients with pernicious anemia in relapse contain large amounts of vitamin B_{12} indicates that this material is not destroyed in the gastrointestinal tract and even suggests its synthesis there as a result of bacterial action. Indeed, extracts of the stools of untreated patients with pernicious anemia containing vitamin B_{12} have been shown by Bethell and his associates to cause significant hematologic and clinical responses upon intramuscular injection into other patients with pernicious anemia. The demonstration of vitamin B_{12} in cow manure, sheep rumen and sheep feces also strongly suggests that it is synthesized by bacterial action in the gastrointestinal tract and that in man such action occurs at the lower end of the intestinal tract, where it finds no ready avenue of absorption.

Callender and her colleagues[171] have confirmed the presence of vitamin B_{12} in the feces of a patient with pernicious anemia in relapse and have noted that it behaves in chromatographic studies as purified liver extract.

Since there is no evidence that vitamin B_{12} is destroyed, the question arises why this water-soluble material, present as it is in a number of foods, is not absorbed and why patients ever develop pernicious anemia when partaking of a reasonably adequate diet. Berk and his co-workers,[141] accordingly, decided to determine whether the effect of vitamin B_{12}, given by mouth in suboptimal doses (5 microgm.), could be potentiated by the administration of normal human gastric juice. Such potentiation was clearly demonstrated in 4 carefully controlled cases. However, as with liver extracts, the activity exhibited by vitamin B_{12} and gastric juice taken orally was still not as great as that of the same quantity of vitamin B_{12} alone given parenterally. This work, which has been confirmed by Hall et al.[172] and more recently corroborated for vitamin B_{12b},[48] suggests that the extrinsic factor, rather than being the precursor of the anti-pernicious-anemia principle, is identical with or closely related to vitamin B_{12}. It thus appears that the intrinsic factor is necessary in man for effective utilization of the relatively small amounts of vitamin B_{12} or closely related substances that are present in most foods. Liver happens to contain a high concentration of vitamin B_{12} and is therefore effective without the intrinsic factor. Castle and his associates[173, 174] have recently prepared extracts of beef muscle that are suitable for parenteral administration. These extracts manifest hematopoietic activity when given parenterally in pernicious anemia and also support the growth of *L. lactis*. This observation, confirmed by Morgan, Byron and Campbell,[175] further supports the hypothesis that extrinsic factor and the antipernicious-anemia principle are identical or closely related. It thus appears probable that the function of the intrinsic factor of normal human gastric juice is to facilitate the absorption by the intestine of vitamin B_{12}, or chemically related compounds in food, rather than to react with the extrinsic factor in the elaboration of the antipernicious-anemia principle.

Differential Diagnosis

Although the differential diagnosis of pernicious anemia is not difficult in the well marked case, many other blood disorders, especially refractory anemias, may closely simulate this condition. Gastric anacidity is demonstrable in at least 99 per cent of patients with classic Addisonian pernicious anemia. Obviously, however, it is a purely nosologic conceit to maintain that the presence of free hydrochloric acid in the gastric secretion excludes the diagnosis of pernicious anemia, because it has now been established that anemias responding specifically to vitamin B_{12} may exist although free hydrochloric acid is present. The association of glossitis and neural manifestations involving the posterior or lateral columns, or both, together with a macrocytic anemia, may be considered as almost unequivocal evidence for the diagnosis of pernicious anemia. However, all too often patients in the early stage of the disorder fail to present all these manifestations, and since it is of the utmost importance to initiate treatment early to prevent the development of irreparable damage to the nervous system it may be worth while to attempt a therapeutic test. This is accomplished as follows: the blood is examined daily for three or four days, with particular attention to the number of reticulocytes; if these remain at a relatively constant level, on the fourth or fifth day, 50 *U.S.P.* units (injectable) of liver extract or 50 microgm. of Vitamin B_{12} is administered in a single intramuscular injection (10 *U.S.P.* units of liver extract or 10 microgm. of vitamin B_{12} may be injected daily for five days as an alternative procedure). The reticulocytes are carefully enumerated daily, and complete blood values obtained every few days for a period of ten days. Barring complications such as azotemia of severe degree or marked febrile sepsis, patients with true pernicious anemia whose initial red-cell level is 3,500,000 or lower will show a characteristic reticulocyte and red-cell response. The reticulocytes begin to rise between forty-eight and ninety-six hours after the initiation of treatment. They reach a peak (the height of which is inversely proportional to the initial red-cell level) on the fifth to tenth days and then subside slowly to a low level during the second or third week. At the height of the reticulocyte response the red cells and hemoglobin begin to rise and continue to do so steadily until normal values are established. The rate of rise of the red cells and hemoglobin is likewise dependent on the initial red-cell values. The absence of a characteristic response of reticulocytes and red blood cells in an anemic patient is almost certain evidence, barring the complications mentioned above, that the patient does not have pernicious anemia. It is of course of paramount importance that no other form of treatment for anemia be administered while the therapeutic trial with liver extract is under way.

Treatment

It cannot be stressed too emphatically that the diagnosis must be firmly established, since once adequate treatment has been started and the blood has returned to normal, there is no way now available by which the diagnosis can be subsequently corroborated other than by omitting treatment and waiting weeks or months for relapse to occur. This is a dangerous procedure in view of the possibility of fulminating and irreversible neurologic damage. Transfusion of blood is indicated if a

severely anemic patient shows circulatory failure or air hunger or if complications such as serious sepsis or azotemia exist to suggest that a satisfactory response to liver therapy alone cannot be expected. The therapeutic test outlined above is a perfectly satisfactory way of initiating treatment even in cases in which the diagnosis is quite clear. After the initial administration during the first week of 50 *U.S.P.* units of liver extract or 50 microgm. of vitamin B_{12} it is wise to administer 15 *U.S.P.* units of liver extract or 15 microgm. of vitamin B_{12} by injection once weekly until the blood values are entirely normal. If there is considerable involvement of the nervous system it may be advisable to continue with weekly injections for the first year. Otherwise, it is generally recommended that injections be given every two weeks for the remainder of the first year, and thereafter the frequency diminished to once every four weeks. Although a few patients may require injections more often than once in four weeks and some may be maintained in a continued state of good health with injections at intervals of six weeks or more, there seems little to be gained by experimenting with intervals longer than four weeks. The advantages of giving liver extract or vitamin B_{12} by injection as opposed to the oral route are many; in the first place, the quantity required is far less than that necessary by mouth, and accordingly the expense is markedly reduced; secondly, the factor of intestinal impermeability is circumvented; and, thirdly, the physician, having injected the potent material, knows that it is effectively within the body and need not fear oversight in treatment on the part of the patient.

A well balanced, nutritious diet is advisable for all persons whether sick or well. Such a diet, therefore, should be encouraged in patients with pernicious anemia, but no other special dietary regime is indicated. Occasionally, pernicious anemia will be associated with an iron deficiency. This will become manifest after a month or two of treatment with liver extract by the appearance of a definitely hypochromic blood picture. In such cases diligent search should be made for possible occult blood loss from the gastrointestinal tract. Should a bleeding lesion of any type be found, it is imperative that this be treated. The iron deficiency may be corrected by the administration of 0.3 gm. (5 gr.) of ferrous sulfate three times daily for a period of one month. In the absence of continued bleeding this will correct any iron deficiency that may be present, and need not be continued longer.

The working hypothesis that is suggested is that, for the most part, there is a quantitative reduction in the functioning of one or more enzyme systems in the macrocytic anemias rather than the total and complete absence of any enzyme. It is thought that the final defect leading to megaloblastic arrest of the bone marrow, manifested as a macrocytic anemia, may be the same in Addisonian pernicious anemia, the macrocytic anemia of pregnancy, tropical macrocytic anemia, the macrocytic anemia of fish tapeworm infestation, intestinal short circuits, stenoses and so forth.[176] This defect is considered due to the inability of the organism to synthesize a material necessary for the maturation of red blood cells (as well as for the proper functioning of many other tissues), and it is believed that this synthesis represents a complex chain in which many enzyme systems are involved. In one such system pteroylglutamic acid and in another vitamin B_{12} may be the prosthetic group. Information at the moment of writing is so fragmentary that it seems unwise to speculate about the substrates of these reactions. Eighteen years ago the concept that nucleic acid or nucleoprotein metabolism was involved in the pathogenesis of pernicious anemia was considered sufficiently attractive to merit investigation[176]; the results at the time were negative. Certainly, microbiologic evidence today indicates that both pteroylglutamic acid and vitamin B_{12} are intimately associated with the synthesis of nucleic acid precursors.

A hundred years have elapsed since Addison first described the disease named by Biermer some years later "progressive pernicious anemia," and it is a quarter century since Minot first demonstrated the effectiveness of a "special liver diet" in its treatment. There appears to be little doubt that the disease is a nutritional deficiency conditioned by the state of the gastric secretion, and it is likewise evident that this and related clinical syndromes may be dependent upon a lack in the diet or upon faulty absorption or utilization of one or more dietary factors. Further chemical, physical and biologic study, combined with clinical investigation at the bedside, may confidently be expected to unravel many of the remaining obscurities in the next twenty-five years.

Publications concerning vitamin B_{12} follow one another so rapidly that many will no doubt appear before this review is printed. No papers appearing after December 31, 1949, have been included. I am indebted to Miss Marion Draper for her invaluable bibliographic assistance.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 36321

PRESENTATION OF CASE

First admission. A seventy-five-year-old man was admitted to the hospital because of the sudden onset of severe right-upper-quadrant abdominal pain that radiated around to the back. There was nausea and vomiting but no alteration of bowel habit, and the patient denied previous gastrointestinal symptomatology. There was no jaundice. Examination showed evidence of atelectasis of the right lower lobe, and there was rebound tenderness and muscular spasm in the right upper abdominal quadrant. The leukocyte count was 12,900, with 94 per cent neutrophils. The patient was treated expectantly for two weeks, following which the abdomen was explored. The gall bladder was empyemic and communicated with an abscess in the lesser peritoneal sac through a rupture in the ampulla. By dissection extending from the fundus downward it was possible to liberate and remove an estimated three fourths of the gall bladder. In addition to dark-brown purulent material the gall bladder contained numerous calculi. The common and cystic ducts apparently were not visualized. The wound was closed with drainage. The postoperative course was relatively uneventful, the wound healed well, and the patient was discharged in fair condition, with minimal residual tenderness in the right upper quadrant.

Final admission (five years later). On returning home the patient regained his strength and lived an active, symptom-free life. Two months prior to readmission, however, he noted the insidious onset of fluctuating but gradually progressive jaundice associated with pruritus and listlessness. One month prior to admission he began having nonradiating soreness in the right upper abdomen every afternoon, unrelated to meals and lasting for one hour. Two weeks prior to admission the stools became clay colored, and a week later the urine became dark. There was a slight tendency to diarrhea and urinary frequency. There was nocturia (two or three times). A 10-pound weight loss occurred over the two-month period. Alcoholic intake had been limited to an occasional glass of beer.

Physical examination revealed a well developed, well nourished, deeply icteric man in no distress.

Excoriations were noted over the chest and arms, but there were no angiomas, "liver palms" or axillary epilation. Slight dullness was elicited at the posterior base of the right lung, and a few sticky rales were heard in this area. The heart was normal. The abdomen was distended, without evidence of fluid. There was fullness in the right upper quadrant, but no organs or masses were palpable. The prostate was three times the normal size.

The temperature was 99°F., the pulse 65, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

The urine had a specific gravity ranging from 1.012 to 1.014 and gave a ++++ test for bile. The urobilinogen was 0.35 Ehrlich units. The hemoglobin was 15 gm. The leukocyte counts ranged from 11,000 to 15,000, with 75 per cent neutrophils. The stools were clay colored, with a ++ guaiac reaction on one of two examinations. The serum van den Bergh was 20.0 mg. per 100 cc. direct, 31.2 mg. total; the alkaline phosphatase was 8.0 units, the cholesterol 156 mg., and the cholesterol esters 45 mg. per 100 cc. The prothrombin time was 36 per cent of normal, and the cephalin flocculation ++ in twenty-four hours and +++ in forty-eight hours. The total protein was 5.42 gm., the albumin 2.89 gm., the globulin 2.53 gm., the nonprotein nitrogen 38 mg. and the amylase 38 units per 100 cc., and the lipase was 1.4 cc. X-ray studies of the abdomen showed no opaque stones in the region of the gall bladder. A gastrointestinal series revealed a small hiatus hernia and questionable extrinsic pressure on the duodenal loop. Chest films disclosed a diffuse miliary pattern of nodular densities best seen in the right-lower-lung field. Streaky density was noted in the region of the left lower lobe, and the right middle lobe appeared somewhat small. An electrocardiogram showed widespread T-wave changes that were thought to be due probably to coronary-artery disease.

The patient was placed on a regime of bed rest, high-calorie diet, added vitamins and large doses of vitamin K. With this the prothrombin time rose slowly to normal over a period of six days. A sigmoidoscopic examination was negative, and an aspiration liver biopsy was reported as showing bile stasis. The jaundice continued, and the chemical findings in the liver remained essentially unchanged. Because of suspicion of early cardiac failure the patient was digitalized. On the ninth hospital day his condition deteriorated, and he became disoriented and stuporous. The nonprotein nitrogen rose to 83 mg. per 100 cc.; the carbon dioxide was 17.6 milliequiv. per liter, and the pH was 7.3. Coma ensued on the tenth hospital day. Nutrition was maintained by gastric intubation but all restorative measures failed, and the patient died quietly on the eleventh hospital day.

Differential Diagnosis

Dr. Leland S. McKittrick*: Dr. Wyman, I have to sink or swim on what you tell me. Do you want to show us the films? I hope you are generous this morning!

Dr. Stanley M. Wyman: The films of the chest show chiefly atelectasis in both lower lobes. I am not too impressed by the somewhat nodular density described in the protocol, and I would think there was no definite intrinsic disease in the lungs. The heart is probably hypertensive or at least arteriosclerotic. The one film that we have of the right upper quadrant shows no opaque gallstones. The gastrointestinal series demonstrates a small, rounded defect in the medial aspect of the duodenum that is seen on at least one spot film. Unfortunately, this area is not included on the other large film. I think this raises the old question of a lesion in or near the ampulla of Vater. It may represent a common-duct nonopaque stone, a small papilloma or other tumor, or perhaps disease of the head of the pancreas.

Dr. McKittrick: Thank you. I never can get much help out of you fellows when I am on the spot.

There are two problems: to make a diagnosis, which I am unable to do with any degree of assurance, and to decide why the patient died, which I am also unable to do with any conviction.

This record contains a good many laboratory tests and not a great deal of clinical information. I would like to know if there was evidence of a fever and how much urine the patient was excreting. I know the specific gravity; was there anything else in the urine?

Dr. Tracy B. Mallory: Here is the chart.

Dr. McKittrick: There was no fever. The chart does not record the urinary output. That is interesting. I always thought the urinary output in a man who had a question of liver disease was very important in following the course, but perhaps I am old fashioned about this. I had been taught to follow the urinary output carefully. If it went down and down, the attending physician got more and more apprehensive; if it went up and up, he began to breathe a sigh of relief.

This man was eighty years old. Everything may be "haywire" in a patient of this age. The responses to stimuli of any kind are not those of a younger man. Whenever I see an eighty-year-old man who has something serious the matter with him, I look for a good deal of trouble on very little evidence. I think there was a great deal going on here that might not have been reflected in the clinical evidence. He had one operation five years previously without any trouble. The history is probably consistent with a common-duct stone and is perfectly consistent with carcinoma or intrahepatic disease as far as I can see. The laboratory

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tests, as I interpret them, certainly suggest that the patient has some interference with liver function. From the evidence at hand I would not have thought that the liver-function disturbance alone was sufficient to have caused his death.

We must first try to decide whether this man had obstructive jaundice or jaundice due to intrahepatic disease. If we can decide between these two conditions, it begins to cut things a little finer. We must accept some degree of intrahepatic disease on the basis of the laboratory data. The alkaline phosphatase was neither here nor there. A lowered cholesterol and a lowered prothrombin level, with the slow return to normal, suggest that the liver was not functioning normally. The total protein was a little low, perhaps because of starvation, but the albumin-globulin ratio was approaching the line where it was suggestive of liver disease. There was nothing in these data to suggest pancreatitis. The amylase and lipase were of no great significance. I think we can assume that the patient had mild liver disease.

Right now I am impressed by the importance of going to staff meetings. A few days ago I heard Dr. Daniel S. Ellis reporting on liver biopsies at the Deaconess Hospital staff meeting. I left that meeting with the impression that when Dr. Mallory's Department makes a positive statement about a liver biopsy, we ought to pay attention to it. This patient had a liver biopsy, and bile stasis was reported. Because of what Dr. Ellis said and because this interpretation fits in with my interpretation of other evidence I am going to accept it. On the basis of the history and on the basis of jaundice of two months' duration, as well as liver-function tests that are no worse than these and a liver biopsy showing bile stasis, I am willing to put the primary cause of the difficulty as obstruction to the biliary flow, with secondary involvement of the liver.

Now comes the next question, Why did this patient have obstruction to the bile flow? A logical reason in this elderly man would be a hangover from the old condition, but it also might be due to a new condition such as carcinoma. Of course, it becomes purely a matter of guessing just how to play the cards. This patient had quite a piece of the gall bladder left. He obviously had had a stone, which was impacted and had eroded through the gall bladder because of the abscess around its ampulla. This can be no criticism of the surgeon if I suggest that quite possibly a stone was left in that gall bladder remnant. It is also possible that this man could have gone for five years without any trouble before the stone went down into the common duct. The absence of pain is in no sense contradictory to the possibility of a stone in the common duct because these elderly people, particularly with a chronic process of this sort, may have the duct obstructed with very little or no pain. I would be happier if the patient had had chills and fever, but he did not have. But this is just one possibility.

Another very real possibility that would have to be given serious consideration is the development of carcinoma in the remnant of the gall bladder. We all know that carcinoma of the gall bladder is extremely rare in the absence of gallstones, but this patient had an extensive inflammatory process and there may have been one or more stones left in the bladder. It certainly seems within the realm of logic that cancer could have developed in that gall-bladder remnant or in relation to the ampulla of Vater, or in the head of the pancreas. The single ++ guaiac test suggests that there was an ulcerated lesion in the gastrointestinal tract somewhere. However, I do not think that a single ++ guaiac test can be taken too seriously.

I do not see how I can logically make a diagnosis differentiating a stone, a carcinoma arising in the old remnant of the gall bladder and a new lesion arising in the ampulla of Vater. I am intrigued by the shadow that Dr. Wyman pointed out. It makes me wonder whether a large stone in relation to the ampulla might cast a shadow that was comparable to that found — particularly with barium over a stone, concentric rings might not be found.

Dr. Wyman: We were thinking in terms of a nonopaque stone if this was a stone.

Dr. McKittrick: I do not know, but I would think this man had a background for a stone, and since I do not know of any sound way to distinguish among the three things I mentioned, I might just as well say that a stone left at the time of the operation settled in the common duct, became impacted and was responsible for the jaundice.

But I still have not explained the death, and I do not think I can explain it with complete satisfaction. There is nothing in the record to help me. I do not know what it was that suggested cardiac failure. I suspect that there must have been a certain amount of sepsis along with the stone, if there was a stone. I am inclined to believe that this was an old man who had just a little bit more than he could take and died from a combination of secondary liver disease and renal disease, probably more severe than might have been evident from the nonprotein nitrogen of 38 mg. per 100 cc. Dr. Mallory, the best I can do is guess that there was obstructive jaundice due to a stone that was left at the time of the old operation and that the patient died of a combination of things that old men die of, the primary cause of death being in the liver and the kidneys.

Clinical Diagnoses

Cholemia.
Biliary calculus.
Uremia.

Dr. McKittrick's Diagnosis

Stone in common duct, with secondary intrahepatic disease.

Anatomical Diagnoses

Carcinoma of remnant of gall bladder, with extension into hepatic ducts.
Choledocholithiasis.
Lipoma, duodenum.
Pulmonary atelectasis and edema, marked.
Pulmonary emphysema, moderately severe.
Coronary sclerosis.

Pathological Discussion

Dr. Mallory: At autopsy we found that there were stones in the common duct, several small ones, but they were in a pocket-like diverticulum of the duct and were not obstructive. The filling defect shown by Dr. Wyman turned out to be due to pedunculated lipoma in the lumen of the duodenum, which hung down loosely over the papilla but, again, was not obstructive. There was practically complete biliary obstruction, however, due to a mass of carcinomatous tissue that occupied the general region of the gall-bladder bed at the junction of the two hepatic ducts. It would be impossible to say whether the tumor was primary in the remnant of the gall bladder that we know was left behind at the first operation or in one of the hepatic ducts. We thought that the best possibility was that it originated in the remnant of the gall bladder. There was a moderate degree of biliary cirrhosis and relatively mild infection. There were both severe atelectasis and terminal pulmonary edema. The coronary arteries were sclerotic, but there were no points of occlusion, and although he had marked arteriosclerosis of the aorta, it did not seem to be in any vital spot. He did have a great deal of pulmonary atelectasis and edema as well as moderately severe pulmonary emphysema.

CASE 36322

Presentation of Case

First admission. An eleven-month-old boy was admitted to the hospital because of torticollis of about seven months' duration.

The patient was born uneventfully, without instruments, after seven hours' labor. The mother's health during pregnancy had been good. The infant appeared normal at birth, and his feeding and early development were normal. At about three or four months of age, it was first noted that the head was tilted to the left, with rotation of the chin to the right. This condition became gradually worse despite treatment with a supportive collar and passive stretching exercises.

The family history was noncontributory.

Physical examination showed the patient to be well developed and well nourished. The head was inclined to the left about 45° from the vertical plane, and the chin was turned to the right. This posture was maintained on flexion and extension of the neck. The right sternocleidomastoid muscle was thin and lax, and the left was well developed and somewhat shortened but not especially tense. The left posterior neck muscles were likewise thought to be shortened. The spine and limbs were normal, as were the tendon jerks and the abdominal and plantar reflexes. There were no other physical or neurologic abnormalities.

The temperature, pulse and respirations were normal.

Examinations of the blood and urine were normal. X-ray films of the cervical spine showed questionable widening of the vertebral canal, but no other abnormality. Skull films were not entirely satisfactory but appeared normal. On lumbar puncture (on two occasions) clear cerebrospinal fluid under normal pressure was obtained. The fluid contained no cells and 71 mg. per 100 cc. of total protein. Electric stimulation showed the left sternocleidomastoid muscle to contract much more strongly than the right. Electromyograms showed constant activity in the left neck muscles but no evidence of a lesion of a lower motor neuron. Under general anesthesia movements of the cervical spine were found to be unrestricted. The optic disks and retinas, likewise examined at this time, were normal. Myelography with iodized oil and with air disclosed no subarachnoid block and no abnormality of the spinal cord. An electroencephalogram was normal.

The patient was discharged with a corrective collar and recommendations for exercises and was followed in the Out Patient Department.

Second admission (three months later). The patient had remained in good health, but the abnormal posture of the head persisted unchanged. He was readmitted to the hospital for further study.

Physical examination showed the patient to be somewhat undersized and fretful and irritable. The tilting and rotation of the head were as before. He could walk only with assistance, with a broad-based, unsteady gait. He could stand unsupported but unsteadily. Physical and neurologic findings were otherwise unchanged.

Lumbar puncture demonstrated a clear fluid under a pressure equivalent to 200 mm. of water and containing 4 lymphocytes per cubic millimeter and a total protein of 160 mg. per 100 cc.

A repeat x-ray examination of the cervical spine showed no change. After several examinations, rendered difficult by the patient's inability to cooperate, it was decided that ocular fundi and eye movements were normal. Air myelography and pneumoencephalography were carried out. No abnormality of the cervical spinal canal or cord was seen. The lateral ventricles were considerably en-

larged, and the fourth ventricle was displaced forward of its normal position.

On the twenty-ninth day an operation was performed.

Differential Diagnosis

Dr. Ralph A. Ross*: In summary, an infant born perfectly normally, without any evidence of abnormal stress first showed signs of torticollis at the age of three months. A diagnosis of local muscle disease — a congenital or traumatic injury to the sternocleidomastoid muscle with shortening — was made, and the proper treatment of stretching the muscle and maintaining the head in good position was instituted. At the age of eleven months there had been no improvement in this condition. There was, however, no evidence of other neurologic deformity on admission to the hospital. There was definite increased activity on the affected side and laxness of the muscles in the opposing group that was apparently considered due to the constant stretching. There was free mobility. X-ray films of the spine and the skull were taken at that time. Do you have those films, Dr. Wyman?

Dr. Stanley M. Wyman: These are only reasonably good films of the skull, but the skull seems to be normal in contour and without evidence of increased pressure or widening of the sutures. The spine curves toward the left, and I believe there is a suggestion of some widening of the cervical canal both anteroposteriorly and laterally. Unfortunately, the films of the later examinations, the encephalogram and myelogram, are not at hand.

Dr. Ross: I am, therefore, not aided in diagnosis by this x-ray examination except that there is no clearcut evidence of increased intracranial pressure, which should be shown at this age by separation of the sutures. The widening of the vertebral canal is not borne out by the finding of any abnormal structure by the contrast medium as described in the protocol. Were any head measurements taken at the two admissions that might indicate the development of increasing intracranial pressure? One would expect a growth normally of 2 or possibly 3 cm. in three months, but not more.

Dr. Allan M. Butler: No head measurements were taken.

Dr. Ross: At thirteen months of age the child was readmitted with the additional findings of increased irritability and a broad-based gait. I wonder how much significance to attribute to symptoms of unsteadiness at the age of thirteen months. Inasmuch as this child was just beginning to learn to balance, it would be a little difficult to evaluate his ability to walk. A broad-based gait would be unusual in a child just starting to walk and probably was of significance. The spinal-fluid pressure on the second examination was slightly above the upper limits of normal, but in a child of thirteen months who is struggling, as almost invariably happens, the reading is of no great significance. However, the rise in cerebrospinal-fluid total protein from the original reading of 71 mg. to 160 mg. per 100 cc. some months later suggests the presence of some irritative lesion in the central nervous system. The next information of importance is that no pneumoencephalomyelographic evidence of a lesion in the cervical column was elicited, but there was a displacement forward of the fourth ventricle, with lateral ventricles enlarged, — in other words, evidence of a space-occupying lesion in the posterior fossa, — with some block in the ventricular system.

Could a space-occupying lesion in the posterior fossa explain the whole picture, the broad-based gait being due to some lesion in the cerebellum? Yes. The irritability of a child is a hard thing to define, but certainly increased intracranial pressure with headache may express itself simply as increased irritability in a child of this age. The torticollis of nine months' duration is rather hard to accept on the basis of a lesion present in the posterior fossa for this time. It must represent the excitation of the nerve due to infiltration or pressure or possibly a cerebellar ataxia, which in my limited experience does not seem likely. However, we will be instructed in that, I am sure, by more proficient observers. Therefore, without the benefit of seeing the films, but accepting the statement in the protocol, I believe there was a space-occupying lesion in the posterior fossa.

Could the lesion have been due to infection? There was no evidence that the tuberculin test or blood Hinton test was positive. Either tuberculosis or syphilis might produce a granulomatous lesion. A pyogenic abscess of this duration would be unlikely, and there was no evidence of any infection. I shall therefore dismiss that possibility.

That leaves me with the possibility of a tumor in the cerebellum. A tumor in the cerebellum of an infant progressing for nine months without producing more obvious symptoms than this is probably a slowly growing tumor. If it was a slowly growing tumor, at this age statistically it probably was an astrocytoma. If the symptomatology of the torticollis was not related and there were two separate diseases, this could have been a more malignant type of tumor, such as a medulloblastoma. However, I will leave my diagnosis as cerebellar tumor, probably astrocytoma, producing cerebellar ataxia with torticollis.

A Physician: I wonder if you would add a dermoid cyst?

Dr. Ross: It is fair enough to say that one can go through a whole list of possible lesions that might occur. I mentioned these two tumors because of the statistical chances.

Dr. Bertram Selverstone: I believe it would be rather unusual to have a total protein of 160

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mg. per 100 cc. with a dermoid cyst. That suggests a more actively neoplastic lesion.

DR. TRACY B. MALLORY: Dr. Selverstone, would you tell us the opinion on the ward?

DR. SELVERSTONE: We were very puzzled by this whole picture, and the diagnosis was not clear in our minds until we had done the pneumoencephalogram that showed just what was described. Although there was some disagreement among the radiologists, there was generally thought to be an anterior displacement of about 1 cm. of the fourth ventricle, whose outline was otherwise fairly normal. We therefore believed that we were dealing with a cerebellar tumor. In view of the long history we thought, as Dr. Ross did, of an astrocytoma or possibly of a dermoid cyst in spite of the unusually high protein. We also considered the possibility of involvement of the accessory nerves as a cause for the torticollis.

DR. MALLORY: Would you like to comment on the clinical features, Dr. Kubik?

DR. CHARLES S. KUBIK: There were some interesting features about the case that might be mentioned. The head could be straightened out, partly at least, without an anesthetic. It seemed to me that the position of the head was not due to muscle spasm or paralysis. The patient always assumed the same position, lying face down with his rear end up in the air and his head down against the pillow and flexed acutely to one side. That, together with the nystagmus and the unsteady gait, suggested a lesion in the posterior fossa, possibly causing a disturbance of the postural reflexes. I have never seen another case like this. Tumors of the posterior fossa are not very uncommon, and there is usually a little tilting of the head, but nothing like this.

DR. SELVERSTONE: Most of us thought there was a reduction in the bulk of the posterior cervical muscles on the right as compared with the left, and we thought that there was some spasm of the left posterior neck muscles as well. As noted in the protocol, we also considered the right sternocleidomastoid muscle to be diminished in bulk as compared with that on the left. I might add that there have been 2 similar cases to my knowledge at the Children's Hospital within the past few years.

CLINICAL DIAGNOSIS

Tumor of posterior fossa.

DR. ROSS'S DIAGNOSIS

Astrocytoma of cerebellum.

ANATOMICAL DIAGNOSIS

Astrocytoma of cerebellum.

PATHOLOGICAL DISCUSSION

DR. MALLORY: We might look at the pictures of the operation, Dr. Selverstone.

DR. SELVERSTONE: On the slide taken at operation before the arachnoid was opened, the medulla is grossly expanded and extends down to the lower border of the lamina of the second cervical vertebra. The medulla was diffusely widened and discolored, slightly more on the left side than on the right. When the arachnoid was opened, lying just beneath was a tumor, which appeared to arise from the closed part of the medulla. It extended into the lower part of the fourth ventricle and formed a collar around the medulla. The tumor could be followed around to the point where it was actually in contact with the accessory nerves of either side as well as with the cervical nerve roots. There was, as is commonly the case, no posterior root of the first cervical nerve, but its anterior root and both the anterior and posterior roots of the second nerve as well were involved. The tumor appeared greasy and was gray. It was impossible to remove the tumor entirely because of its very firm adherence to the closed portion of the medulla and to the floor of the fourth ventricle. Accordingly, I would guess that I was able to remove from 50 to 70 per cent of the lesion. I left an extensive decompression.

DR. KUBIK: The tumor was an astrocytoma. Was it cystic?

DR. SELVERSTONE: It was entirely solid.

DR. ROSS: Was the torticollis due to irritation of the nerve or to paralysis?

DR. SELVERSTONE: It is hard to say. One might speculate that there might have been irritation of the left nerves and paralysis of those on the right.

DR. KUBIK: How is the patient now?

DR. SELVERSTONE: Postoperatively he was much less irritable than before, and he seemed much happier. He was given x-ray therapy and a month after operation was discharged. I do not think that any apparatus should be used in an attempt to correct the torticollis. It has not improved since operation.

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The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

MEDICAL OFFICERS NEEDED!

The *Journal* of August 3 contains a communication from Dr. Thomas R. Goethals emphasizing the present urgent need of the Army for medical personnel. This letter, while of general interest to the medical profession, is expressly concerned with those young physicians who not only were deferred from Selective Service during World War II but received in addition financial aid from the Government to complete their medical education.

Most of these young men were wisely exempted from the hardships and the hazards of the recent war in order that they might keep from depletion the ranks of an essential profession; their opportunity has now come to volunteer for the privilege of serving those fellow Americans who are shedding their blood upon a foreign soil.

The appeal of General Goethals is not inconsistent with Bradford's plea, published in the same issue, for the proper use of medical personnel. Bradford pleaded for an over-all flexibility in the employment of the entire medical profession, under one central authority, that would recognize the need where the need was greatest, whether for service with troops or for civilian defense on an equally important battle line. The present call is on a group especially fitted by age and recent training to serve a particular part of the over-all program. The need is imperative; the threat to freedom everywhere is obvious; the response must be immediate.

Fortunately, the mistakes of World War II are so recent that some of them may still be reviewed with profit. Its avoidable wastage in men and material *must* be reduced. The directors of national defense are under the most solemn obligation to act with wisdom and foresight in the use of the country's resources. Stupidity in places of authority must be eliminated, in the face of so much responsibility. Democracy must function well or fall. There must be no chance that trained medical officers will be detailed to inspect latrines on uninhabited islands in the Pacific.

If the present battlefront is extended to the degree that is easily possible, this country will be part of it, and the plans that are laid must consider all possibilities and possess the utmost degree of flexibility. Every commitment must be made in force, but the over-all planning must be such that the country will not be sacrificed in the process of mining out of it the men and material to be used ostensibly for its defense.

NATIONAL SCIENCE FOUNDATION

Two previous Congresses having considered measures providing for the establishment of a national science foundation, the eighty-first has finally passed a bill that has met with the approval of the President. Such a bill had been passed by the eightieth Congress and was vetoed. In the present Congress bills were introduced in both houses, and S. 247, after modification, was passed by the House of Representatives on April 27 and by the Senate on the following day and was signed by the President on May 10.

The function of the Foundation is to promote basic research and education in the sciences and to

initiate and support research by making contracts, grants and loans. Research related to national defense will be initiated and supported at the request of the Secretary of Defense; research in the field of nuclear energy will be supported only with the permission of the Atomic Energy Commission. The Foundation will further act as a clearinghouse of scientific information among scientists of the world, will correlate research of individuals and public and private research groups, will maintain a register of scientific personnel, and will present an annual report to the President and to Congress "which shall include minority as well as majority recommendations."

Twenty-four members to be appointed by the President with the advice and consent of the Senate and the *ex-officio* director shall constitute the administrative board; they shall serve for a term of six years and shall be eminent in the fields of the basic sciences. In the making of nominations the President is requested "to give due consideration to recommendations of the National Academy of Sciences, the Association of Land Grant Colleges and Universities, the National Association of State Universities, the Association of American Colleges" and other scientific and educational organizations.

The Director, who shall serve for six years unless sooner removed by the President, will be appointed by the President by and with the advice and consent of the Senate. The Director shall not be appointed until the Board has had opportunity to make recommendations; these recommendations may or may not be heeded.

The Foundation shall consist of four divisions: those of Medical Research, of Mathematical, Physical and Engineering Sciences; of Biological Sciences and of Scientific Personnel. Other divisions, as well as special committees and commissions, may be created by the Board.

The Foundation will establish scholarships and graduate fellowships; it may enter into contracts with organizations or individuals in the United States and foreign countries, including Government agencies; it may acquire and hold property necessary for research, and accept donations; it may publish or arrange for the publication of scientific and technical information. It shall not itself, however, operate any laboratory or pilot plants.

Any recipient of a scholarship or fellowship must file with the Foundation an affidavit that he does not believe in and is not a member of and does not support "any organization that believes in or teaches the overthrow of the United States Government by force or violence or by any illegal or unconstitutional methods and further must take an oath of allegiance to the United States."

For the fiscal year beginning July 1, 1950, $500,000 is authorized, and $15,000,000 annually for each fiscal year thereafter.

Here, in substance, is the National Science Foundation Act of 1950 in which a government seriously mobilizes its resources for the discovery of truth. Truth, however, as no doubt all presidents and all congresses will bear in mind, is a basic quality that depends for its existence on complete intellectual freedom. Truth cannot be regimented and serves no man's bidding.

THE GROWING PROBLEM OF CHRONIC DISEASES

THE first issue of *Chronic Illness News Letter*, the monthly bulletin of the Commission on Chronic Illness, calls the attention of the medical and allied professions to steps being taken to deal with the problem of chronic disease in the United States. In various forms — whether poliomyelitis, tuberculosis, cardiovascular disease, diabetes or any of the other abnormalities that are likely to alter a patient's social and economic activities — these chronic conditions account for three fourths of all illness today.* Progressive control of infectious diseases and the increasing number of elderly people in the population are bringing about a situation in which the chronic illnesses and preventive medicine may in the future demand the entire attention of physicians.

To meet the need for a central organization to study this problem, the Commission on Chronic Illness was founded, with the financial support of the American Medical Association, National Tuberculosis Association, American Cancer Society, American Heart Association, National Society for Crippled Children and Adults, New York Foundation and the National Foundation for Infantile Paralysis. The goals of the Commission are to modify the widely current opinion that chronic illness is hopeless; to define the problems of such diseases in all age groups; to co-ordinate separate programs for specific disease with a general program

**Commission on Chronic Illness: Proceedings of first meeting.* 72 pp. Chicago: the Commission, 1949.

designed to meet the needs of all the chronically ill; to clarify the relations of all groups working in the field; and to stimulate in every locality a well rounded plan for the prevention and control of chronic disease and the care and rehabilitation of the chronically ill (at the second annual meeting in Chicago last May, the Commission recommended that each state, city and major community plan groups to study the problems of prevention, control, care and rehabilitation, and that state medical societies form committees on chronic illness to work with the state-wide planning agency).

A special subcommittee on finance has been appointed to raise financial support in addition to that given by the sponsoring organizations (it has been estimated that the proposed program of education and research will cost $89,070 next year). The Commission wisely decided that the principal contribution should come from many widely representative organizations and private persons.

At present the Commission is gathering information regarding the activities now under way throughout the country. Further administrative research in chronic illness will be carried out as needed. The Commission hopes that its national educational campaign and the co-operative work of the agencies concerned will result in a set of programs for continued concentrated action by local, state and national agencies.

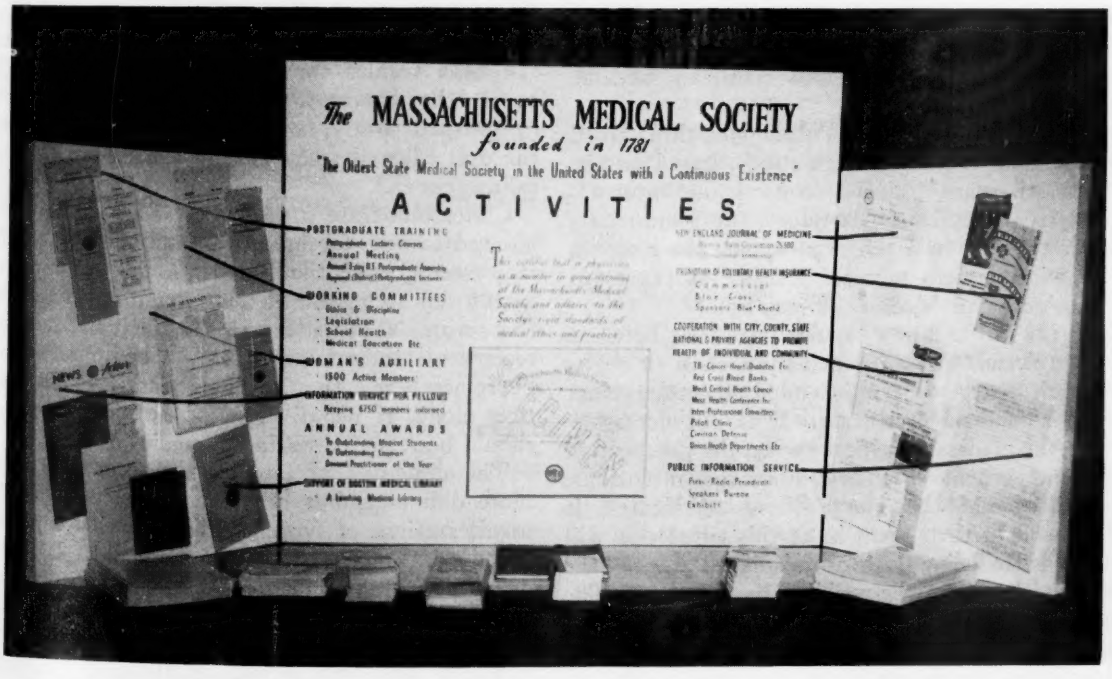
Few more vital programs for the long-term welfare of the American people have been outlined. The Commission on Chronic Illness deserves the active co-operation and financial support of all classes of the population, particularly of physicians, who should appreciate the fact that a voluntary organization has been founded to cope with a problem that gives promise of affecting every phase of medical endeavor.

The present rarity of hydrophobia is mainly to be attributed to the operation of the Act of Parliament, brought in by Mr. Fox Maule, whereby dogs are not now allowed to draw any vehicle in London.

Boston, M. & S. J., *August 7, 1850*

MASSACHUSETTS MEDICAL SOCIETY

EDUCATIONAL EXHIBIT



The Massachusetts Medical Society's first educational exhibit made its debut at the Massachusetts Public Health Conference held in Amherst this past June. Designed to acquaint the general public — and those in the medical and allied fields — with the many activities and scope of the Society, the exhibit will be shown at similar gatherings and conclaves. The center panel of the display is 37 inches high and 48 inches wide, the wings being eight inches shorter and 24 inches wide. Additional educational exhibits are in the planning stage.

POSTGRADUATE CONFERENCE

The Committee on Postgraduate Medical Education announces a postgraduate conference to be held in conjunction with the Massachusetts Department of Public Health at the University of Massachusetts in Amherst, September 13, 14 and 15.

Sessions on atomic warfare medicine and emergency treatment will make up part of the course of instruction, which will be open to all registered physicians.

DEATHS

CARTER — Albert A. Carter, M.D., of Malden, died on June 23. He was in his seventy-sixth year.

Dr. Carter received his degree from Middlesex University School of Medicine in 1917. He was a member of the American Academy of Ophthalmology and Oto-Laryngology and the New England Ophthalmological Society and a fellow of the American Medical Association.

KROBALSKI — Joseph Krobalski, M.D., of Lynn, died on September 3, 1949. He was in his fifty-seventh year.

Dr. Krobalski received his degree from College of Physicians and Surgeons, Boston, in 1924.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PREMARITAL-EXAMINATION LAW

NICHOLAS J. FIUMARA, M.D., M.P.H.*

On February 20, 1950, the Governor signed a bill passed by the Legislature amending the premarital-examination law. This new law became effective on May 21, 1950.

On April 11, 1950, the Public Health Council passed several important regulations, based on the new law, that are designed to carry out more effectively its objectives. Therefore, the basic tenets of both the law and the regulations are more in accord with modern medical practice as expressed by the American Medical Association.[1]

Both the old and new laws require that before a marriage license can be issued by a clerk or registrar, each party to the intended marriage must present a medical certificate. It is not necessary to have the medical certificate when the prospective bride and groom file their marriage intentions, although should they have these certificates, it will be well to turn them in at this time; this will prevent their being lost or misplaced during the hustle and bustle of the wedding preparations. The license will be issued after five days have passed since the filing of the marriage intentions (Sundays and holidays are counted).

MEDICAL CERTIFICATES

The medical certificate may be signed by a physician who is registered and licensed to practice in Massachusetts; registered and licensed to practice in any State or territory of the United States; registered and licensed to practice in Washington, D. C.; a commissioned medical officer on active service with the armed forces of the United States; a commissioned medical officer on active duty with the United States Public Health Service; or a physician licensed to practice in Canada.

The new law has therefore extended the list of acceptable physicians to those in the territories of the United States and in Canada.

OBJECTIVES

The purpose of the law is to discover evidence of syphilis and particularly communicable syphilis in a person who is planning to be married. If, therefore, communicable syphilis is found in the candidate for marriage, he or she will be treated before the wedding takes place in order that this disease may not be transmitted to the noninfected partner and to their children. Although communicable syphilis is the particular target of the premarital-examination law, noncommunicable syphilis should not be neglected.

Arriving at the diagnosis of syphilis in the presence of dark-field-positive primary or secondary lesions should present very little difficulty. Here the problem is one of alertness on the part of the physician and the preparation of suitable material for dark-field examination. This again presupposes a careful inspection and examination on the part of the doctor for the presence of these lesions. To obtain the best results for dark-field examination, the base of the chancre or the secondary eruption should be grasped firmly, and the surface abraded with the dull edge of a scalpel and cleansed with a wet saline sponge.[2]

Under moderate pressure, clear serum should be allowed to ooze forth. A small amount of bleeding may result, and the blood should be wiped off with a dry sponge until clear serum appears. While the serum is being examined, the patient should receive a standard blood test for syphilis. It must be remembered that a single dark-field examination alone, if negative, is of no significance. It should be repeated again and again.

The diagnosis of late syphilis presents a little more difficulty, but here the presence of the late manifestations of syphilis, together with a positive blood test, makes the diagnosis valid. Latent or asymptomatic syphilis, on the other hand, taxes the diagnostic acumen of the physician. It is an exclusion diagnosis and, like all diagnoses based on negative data, the validity of the diagnosis varies directly with the care and skill of the doctor in excluding all other conditions that would give a positive blood test for syphilis. This means that the physician must take a complete medical history and perform a careful physical examination. Reliance cannot be placed on a single positive blood test in the absence of other confirmatory findings.

*Director, Division of Venereal Diseases, Massachusetts Department of Public Health.

Repeated blood tests should be taken to check the original positive laboratory report.

In some cases with no history of previous infection and negative findings on physical examination, particularly in the presence of serologic findings that are of low titer or are conflicting, the diagnosis of the latent or asymptomatic syphilis cannot be safely made. When time is not of primary importance, the patient may be safely followed along, and the serologic pattern observed over a period of several months or even a year. However, when time is of the essence in diagnosis, the physician is advised to turn for assistance to the newly described treponemoimmobilization test of Nelson. Although this test is still in the experimental stage, its value as an additional diagnostic aid is without question.

Approved Laboratories and Tests

Each year the Department approves laboratories in Massachusetts for performing serologic tests for syphilis. These are in addition to the State Wassermann Laboratory. Other than these laboratories the Public Health Council, by regulation, has agreed to accept the results of serologic tests performed by laboratories operated by or for any state health department, Washington, D. C., territories of the United States, New York City, armed forces, Public Health Service and provincial health departments of Canada.

Thus, regardless of where the prospective bride or groom may be living, whether in Massachusetts or anywhere in the United States or Canada, he or she may be conveniently examined by the local physician, and the blood sample tested by one of the acceptable laboratories listed above.

Valid Period of Examination and Blood Tests

The examination, including the laboratory test for syphilis, is valid for thirty days prior to the issuance of the marriage certificate. This thirty-day period should obviate running to the doctor's office at the last minute for the medical examination.

Procedure after Syphilis Has Been Discovered

Should the physician as a result of the examination discover the presence of syphilis in his patient, it will be his responsibility to summon both parties to the intended marriage and inform them of this fact. He must further explain to them the nature of this disease and the possibility of transmitting the infection to the marital partner and to their children.

If the disease is in a noncommunicable stage, the physician is permitted to sign the premarital certificate, although for the sake of the infected person and the spouse, treatment should be undertaken at the earliest opportunity to prevent the development of late syphilis. Should the disease be in a communicable stage or potentially so, however, the physician is expressly forbidden to sign the medical certificate.

Communicable Syphilis

When, then, is syphilis considered to be in a communicable or potentially communicable stage? The Public Health Council has defined this as being the primary, secondary and early latent stages of syphilis. Early latent syphilis has been defined as the presence of a symptomless infection characterized by a repeatedly positive standard blood test for syphilis with negative spinal-fluid serologic findings and with a history of a primary lesion within four years, or in the absence of an initial lesion, when the patient is less than thirty years of age. Although late latent syphilis in a woman of childbearing age is potentially communicable to the fetus during pregnancy, it is not a bar to marriage. However, these women should receive treatment at the earliest opportunity.

Is a person with communicable syphilis barred entirely from getting married? The answer is "no" provided certain conditions are fulfilled. It is recommended that the infected person receive an adequate course of treatment and, after the completion of treatment, that at least a two-year successful post-treatment observation be obtained before marriage. This requires that the marriage be postponed for at least two years.

However, when both partners are unwilling to postpone their marriage, the physician shall issue the premarital medical certificate provided that the infected partner has received, in the opinion of the physician, adequate treatment and provided the other partner to the intended marriage has been informed by the physician of the nature of the disease in the intended spouse, the danger of relapse and the necessity for faithful post-treatment observation.

Under the old law a person with syphilis, whether it was communicable or not, could get married without the benefit of treatment. The new law prohibits such a marriage with a person who has communicable syphilis, unless adequate treatment has been received prior to marriage. The wisdom of this new provision is without question, for in it is expressed the basic philosphy for a premarital-examination law and of good medical practice.

The new law has an additional feature that is a blessing to all who dislike any unnecessary red tape. Under the new law, Massachusetts will accept the premarital certificates of any state or territory of the United States and District of Columbia as well as the provinces of Canada, provided the medical certificate is signed by a physician, licensed to practice in the areas mentioned, who certifies that on the basis of a physical examination and a serologic test performed at one of the acceptable laboratories enumerated above, the person whose name

appears on the certificate does not have syphilis or, if so infected, is not in a communicable stage.

The name of the laboratory performing the test must appear upon the medical certificate, but the result of the blood test need not appear on this form. This is quite a departure from the old law, which required that Massachusetts certificate forms be used by all persons planning to be married in the Commonwealth but examined by a physician in another state.

It is hoped that in the near future all states will agree to accept each others' certificates. Until that day arrives, doctors are cautioned to investigate and determine the requirements of other states, when their patients plan to be married outside Massachusetts. A telephone call to the Division of Venereal Diseases will give the answer in a few moments.

References

1. Editorial. Premarital examination for syphilis. *J. A. M. A.* **139**: 310, 1949.
2. Fiumara, N. J., Gonorrhea and syphilis — standards of diagnosis, treatment and follow-up study. *New Eng. J. Med.* **240**:940-945, 1949.

MISCELLANY

GOLDBERGER AWARD

Dr. Fuller Albright, associate professor of medicine at Harvard Medical School, has been selected by the Board of Trustees and the Council on Foods and Nutrition of the American Medical Association as the 1950 recipient of the Joseph Goldberger award in clinical nutrition.

The award, which consists of a gold medal and $1000 in cash, was established in 1948 to honor physicians who have made important contributions to the world's knowledge of nutrition.

CORRESPONDENCE

CORRECTION ACKNOWLEDGED

To the Editor: The editorial of July 6 concerning the "Apprentice System at Yale" states that a precedent has been set. This would seem incorrect since the University of Wisconsin School of Medicine has had an extensive apprentice system involving one quarter of the senior year, in effect for perhaps ten or more years.

G. A. Nitshe, Jr., M.D.

Philadelphia, Pennsylvania

NOTICES

INTERNATIONAL CONGRESS OF PSYCHIATRY

The International Congress of Psychiatry will be held in Paris, France, from September 18 to 27. The official languages at the Congress will be English, French, Spanish and Russian, with simultaneous interpretations of the addresses during their delivery. The topics on the program include psychopathology, schizophrenia, electroencephalography, endocrine therapy, group psychotherapy and war-induced mental disorders. A program of entertainment, including concerts and evening receptions, as well as trips through Paris and the neighboring countryside, has been planned.

The Congress will be open to all physicians, including psychoanalysts, psychologists and biologists. The headquarters are at 1 Rue Cabanis, Paris XIV, France.

AMERICAN ROENTGEN RAY SOCIETY

The fiftieth annual meeting of the American Roentgen Ray Society will be held in St. Louis, September 26 to 29. The scientific sessions and the scientific and commercial exhibits will be held at the Hotel Jefferson in St. Louis.

The Caldwell Lecture will be delivered on Wednesday, September 27, by Dr. Henry L. Bockus, professor and chairman of the Department of Internal Medicine, University of Pennsylvania School of Medicine. His subject will be "The Role of Roentgenology in Gastroenterology."

AMERICAN PUBLIC HEALTH ASSOCIATION

The Seventy-Eighth Annual Meeting of the American Public Health Association and meetings of thirty-two related organizations in the field of public health and preventive medicine will be held in Kiel Auditorium, St. Louis, Missouri, October 30 to November 3.

The scientific programs under development will be presented by the thirteen Sections which include Dental Health, Engineering, Epidemiology, Food and Nutrition, Health Officers, Industrial Hygiene, Laboratory, Maternal and Child Health, Medical Care, Public Health Education, Public Health Nursing, School Health and Statistics.

GRADUATE INDUSTRIAL HYGIENE ENGINEERING FELLOWSHIP

The James S. Kemper Foundation is offering a graduate fellowship in industrial hygiene engineering at Harvard University, covering tuition and academic fees at the Harvard Graduate School of Arts and Sciences in addition to reasonable living allowances. The successful candidate will work toward the degree of either master of science or master of engineering in the field of industrial hygiene.

In awarding the fellowship, the selection committee of the Foundation will take into account the scholastic record, character, personality and physical condition of candidates, who must first satisfy admission requirements of the University graduate school.

Applications are invited from young men who are graduates of approved engineering, chemistry or physics schools and who are citizens of the United States. They should be addressed to Mr. H. L. Kennicott, Mutual Insurance Building, Chicago 40, Illinois.

UROLOGY AWARD

The American Urological Association offers an annual award of $1000 (first prize of $500, second prize $300, and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists.

The first prize essay will appear on the program of the annual meeting of the American Urological Association, to be held at the Palmer House, Chicago, Illinois, May 21-24, 1951.

For full particulars application should be made to the Secretary, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, New Jersey. Essays must be in his hands before February 10, 1951.

FELLOWSHIPS FOR RESEARCH IN BASIC SCIENCES

The Arthritis and Rheumatism Foundation is offering fellowships for research in the basic sciences related to the study of arthritis. These fellowships carry a stipend of $4000 to $6000, depending upon the needs and ability of the worker, and run for a year. The fellowships would begin in July, 1951, although earlier appointments would be considered by the committee.

The Foundation is anxious to back a candidate, rather than a project, an institution or a hospital. It hopes to arouse interest in arthritis in a wider circle of medical investigators and to encourage able, inquiring minds.

Applications should be sent to the Arthritis and Rheumatism Foundation, 535 Fifth Avenue, New York 17, New York by January 1, 1951. Notification of the fellowships granted will be made on March 1, 1951.

If any applications are received by September 15, 1950, they will be acted on at that time, and notification made immediately.

(*Notices concluded on page xi*)

NOTICES (*Concluded from page 240*)

GRANTS AND FELLOWSHIPS IN CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is accepting applications for grants and fellowships. Applications for new grants will be received until October 1. Investigators now receiving grants will be notified individually regarding application for the extension of these grants. Final decision on grant applications will be made early in 1951. Grants approved at this time ordinarily will become effective July 1, 1951.

Fellowships available include both fellowships in cancer research of the American Cancer Society and Damon Runyon Clinical Research Fellowships, financed by a grant from the Damon Runyon Memorial Fund to the American Cancer Society. Applications may be submitted at any time. Those received prior to November 1 will be acted upon by the Committee on Growth in December. Those received between November 1 and March 1 will be acted upon in April. Fellowships ordinarily will begin July 1, though this date may be varied at the request of the applicant.

During the past year the American Cancer Society, on recommendation of the Committee on Growth, has awarded grants and fellowships approximating $2,000,000. A program of similar magnitude is contemplated for the coming year.

Communications should be addressed to the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, Northwest, Washington 25, D.C.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

AUGUST 28–SEPTEMBER 1. American Congress of Physical Medicine. Page 428, issue of March 16.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 6–MAY 2. Hampshire District Medical Society. Page 170, issue of July 27.

SEPTEMBER 7–9. All-Austrian Congress of Physicians. Page 994, issue of June 22.

SEPTEMBER 14. Progress in the Management of Hand Injuries. Dr. Henry E. Marble. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 18–27. International Congress of Psychiatry. Page 240.

SEPTEMBER 26–29. American Roentgen Ray Society. Page 240.

SEPTEMBER 27. American Medical Writers' Association. Page xi, issue of July 13.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 30–NOVEMBER 3. American Public Health Association. Page 240.

DISTRICT MEDICAL SOCIETY

HAMPSHIRE

SEPTEMBER 6. 4:30 p.m. Belchertown State School.
NOVEMBER 1. 4:30 p.m. Northampton State Hospital.
JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, AUGUST 17

FRIDAY, AUGUST 18
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor Clinic. Out-Patient Department. Mount Auburn Hospital, Cambridge.

MONDAY, AUGUST 21
*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, AUGUST 22
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, AUGUST 23
*12:00 m.–1:00 p.m. Grand Rounds. Amphitheater, Children's Hospital.

*Open to the medical profession.

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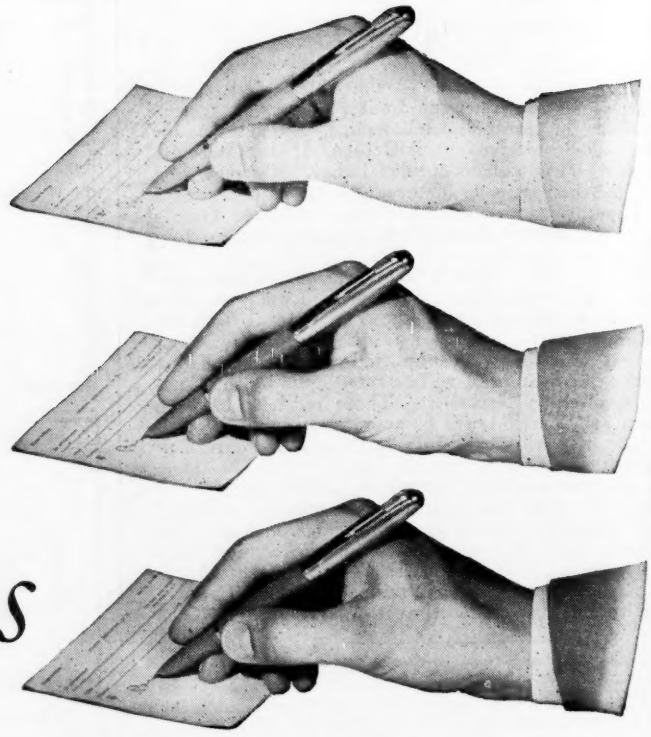
Flexible Formulas

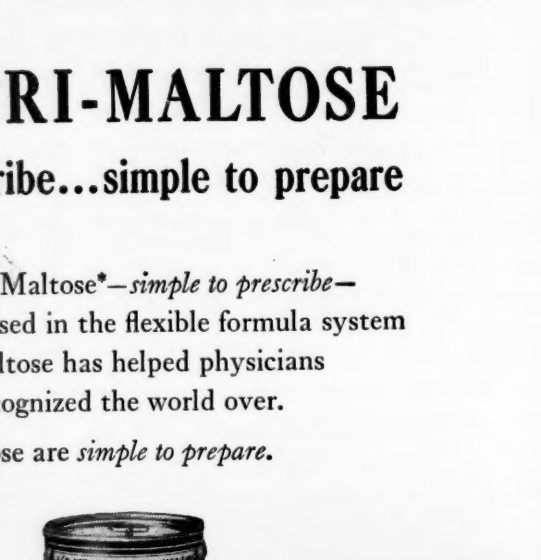


with DEXTRI-MALTOSE

simple to prescribe...simple to prepare

Milk plus water plus Dextri-Maltose*—*simple to prescribe*—is the mixture most widely used in the flexible formula system of infant feeding. Dextri-Maltose has helped physicians to build this system, now recognized the world over.

Formulas with Dextri-Maltose are *simple to prepare.* Dextri-Maltose is easily measured, is readily soluble, and can be used in any method of formula preparation.



*T. M. Reg. U. S. Pat. Off.